EXHIBIT B

Part 1

Report of the Review of Various Documents Relating to Actavis and to the Actavis Product Digitek which is Digoxin.

Other company names and other products are mentioned in the documents provided.

For:
Mr. Peter Miller, Attorney
The Miller Firm, LLC
108 Railroad Avenue
Orange, Virginia 22960
Ph 1-866-529-3323

By:
James J. Farley
Consultant - Smart Consulting Group
101 Captain John's Drive
Savannah, Georgia 31410
Ph 912-898-8505
JJF412@AOL.com
June 14, 2010

SMART CONSULTING GROUP, LLC

Expert Report of James J. Farley
Pharmaceutical Consultant
101 Captain John's Drive
Savannah, GA 31410

Report concerning Actavis
and its various Northern New Jersey locations and its Digitek Product.

For:
Mr. Peter Miller
The Miller Firm, LLC
108 Railroad Avenue
Orange, Virginia 22960
Ph 703-328-7258 Ph 866-529-3323

This report consists of the following sections:

1. Qualifications and Background
2. How the FDA Inspects a Pharmaceutical Company. The Purpose and Nature of Food and Drug Administration Inspections.
3. Documents Reviewed by JJF
4. Additional Reference Sources
5. Comments
6. Conclusions

1. Qualifications

I am a chemist with more than forty years experience in the pharmaceutical industry working for pharmaceutical firms, a pharmaceutical package component supplier, the United States Food and Drug Administration (FDA), and for the last fourteen years as a consultant to the industry. This background provides three distinct points of view of the pharmaceutical industry and its regulations. Details are in my Curriculum Vitae which is Attachment A to this report.

A- Pharmaceutical Industry – As a research chemist I had to be knowledgeable of, and in compliance with, FDA regulations.

B- Pharmaceutical Package Component Producer – I held various positions ranging from Supervisor, Quality Control, to Director, Research & Development. I had to be knowledgeable of, and in compliance with, FDA regulations since our customers were the pharmaceutical firms. Our products, primarily rubber stoppers, had direct contact with drug preparations.

C- FDA – During my time with the FDA in Philadelphia:

I analyzed new and existing pharmaceutical compounds and preparations.

I participated in inspections of firms and in the preparation of Establishment Inspection Reports (EIRs) and 483s. A form 483 contains a list of "Observations," which are violations of regulations.

I directed the activities of a thirty member laboratory staff in analyses of products and in accompanying Investigators on inspections.

I worked at FDA Headquarters for a 30 day detail as Acting Deputy Director, Division of Field Science, during which I interfaced with several FDA Headquarters areas.

At times, when the Philadelphia District Director would be out of the office for a few days, I was Acting District Director, in which capacity I issued Warning Letters and performed many other duties.

For a period of a month, I directed the activities of the Investigations Branch in addition to directing the Science Branch. That is, I was Director of the Science Branch and Acting Director of the Investigations Branch at the same time. This was until a replacement for the promoted and transferred former Director of the Investigations Branch was selected.

I prepared and delivered training courses for FDA staff explaining the pharmaceutical industry and how products are made.

D- Consultant – As a pharmaceutical and FDA regulatory consultant I assist clients in the following areas:

Food and Drug Administration Compliance

- Quality Audits and Implementation of Changes
- Establish/Review Quality Assurance Procedures and compliance with GMPs, including GLPs
- Prepare the Chemistry, Manufacturing, and Controls section of a New Drug Application (CMC section of NDA)
- Prepare Drug Master Files (DMFs)
- Prepare firms for Pre-Approval Inspections (PAIs)
- Process Validation
- Establish program for Corrective Action; Preventive Action (CAPA) including Root Cause Analysis (RCA)
- Establish system for Out-of-Specification (OOS) results and for Deviations
- Consult/assist in responses to FDA Warning Letters
- Consult/assist in responses to FDA form 483s

Technical

- Laboratory Procedures — Development and Validation
- Package/Product Compatibility
- Selection and Testing of Rubber Stoppers and Plastic and Glass Components

Management

- Laboratory Management
- Work Flow Design
- Strategic Planning
- Establish responsibilities and performance criteria for contractor organizations

Training — Design and present training programs in the following:

- Corrective Action; Preventive Action (CAPA)
- Good Manufacturing Practices (GMPs)
- Leadership skills for new managers
- Preparation for an FDA inspection — GMP or Pre-Approval

Background
I am being paid $150/hour from the Smart Consulting Group. I do not know what fee structure Smart Consulting Group has with our client. When on contract with a large firm I accept this instead of the $200/hour usual fee since they have obtained the project and they do the billing.

In the last four years my previous depositions were for:
1- Mainor Eglet Cottle LLP in Las Vegas, Nevada. Deposed in Las Vegas, February, 2010. Henry Chanin, et al. v. Desert Shadow Endoscopy Center et al. Other defendants were Teva and Baxter pharmaceutical companies. Case number 08A571172. Clark County Courts. Eighth Circuit Court of Nevada.

2- Connelly Law in Tacoma, Washington. Deposed in Savannah, Georgia, April 2008. Angela Olson, Plaintiff, vs Septodont, Inc., Burkhart Dental, Inc., Reeve Burkhart Dental Supply Company, Burkhart Dental Supply Company, and John Does 1-5. In The Superior Court of the State of Washington No. 06-2-10742-5 for Pierce County.

I have provided several Subject Matter Expert reports but provided only the depositions above in the last 4 years.

2. How the FDA Inspects a Pharmaceutical Company. The Purpose and Nature of Food and Drug Administration Inspections.

A pharmaceutical company's goal is to produce quality products that will help persons to maintain or regain health. It reinvests the earnings from its sales to continue producing quality drugs for the consumers/patients. The goal of the FDA is to "Protect the Consumer." That is to say that the goal of the FDA is not to help the pharmaceutical company to make a good product but rather to ensure that the firm does not make an ineffective or unsafe product. Note that these

goals are not the same and neither are they opposed. They can be considered synergistic with regard to the safety of the public.

The regulations are contained in The Federal Food, Drug, and Cosmetic Act.
The rules applying to drug firms are listed in Title 21 of the Code of Federal Regulations, parts 210 and 211. This is written as 21 CFR 210 and 211. It contains the information on how to comply with Good Manufacturing Practices (GMPs).

Any drug or drug product component manufacturer must comply with these regulations.
The FDA, in exercising its oversight, does this by periodic inspections. On the one hand, if the FDA never inspected firms at all and simply accepted a company's word that they have been doing things right, there would be no oversight. On the other hand, to have an FDA person present at a particular firm every day would also not be appropriate. The solution to ensuring that the drug firms are complying with the regulations is to conduct periodic inspections of the firms. This is done by one or more Consumer Safety Officers, also called Inspectors, usually accompanied by one or more FDA scientists.

In a GMP inspection the FDA team leader will show the person at the pharmaceutical facility a Form 482 which is a notice of inspection. FDA persons' credentials will be shown. The leader will ask to see the highest ranking person at the facility. Usually a conference room discussion about the management responsibilities, including presentation of an organization chart, follows the introduction. Some firms have prepared slide presentations and binder packages of diagrams and data ready to present to interested parties including the FDA. Next, a tour of the facility is in order. After that, the detailed inspection begins.

The areas covered in the inspection include, but are not limited to, the following:

- Overview of Operations
- Organization and Responsibilities of persons
- Facility tour
- Incoming materials - receipt, inspection, handling, storage, and testing
- Manufacturing, including work-in-progress testing
- Packaging
- Finished goods release testing
- Stability Program for storage and testing of raw materials and finished products
- Validation program - for tests and processes
- Quarantine/reject process
- Line clearance/reconciliation between production runs
- Finished goods inspection/release
- Internal audit program
- Calibration of instruments and equipment and the calibration logs
- Deviation and Out-of-Specification (OOS) Investigation procedures - that is, the Corrective Action; Preventive Action (CAPA) program
- Change control
- Training and the training records
- Batch control management
- Customer complaints

- Adverse Event investigation and reporting system
- Control of specifications

The categories listed above will serve to illustrate many of the areas that must be functioning properly to ensure that the pharmaceutical product is, as FDA requires, of the correct "Identity, Strength, Quality, and Purity."

There are cases where firms are in complete compliance and there are firms where the systems and procedures are not in place. Then there are those firms where the systems and procedures are in place but there is no adherence to them. The inspection reveals what is actually happening at any particular pharmaceutical company.

At the conclusion of an inspection an Establishment Inspection Report (EIR) is written. That can be compared to a trip report in industry. If all is well at the inspected firm then the EIR is sufficient. If there have been "Observations," which are violations, contained in the EIR, they are listed in a separate document. That is the "483" - named because the observations are written on the FDA form 483. Examples of the observations are provided on the form. The persons at the firm at told of these during the exit meeting and are informed that a typed version of the 483 will be sent in the mail to them. They are actually aware during the course of the inspection, since some of the firm's personnel accompany the FDA persons during the inspection.

With the issuance of the 483, the firm is expected to correct the violations promptly. Almost invariably, the firm will respond in writing providing a time frame for when the corrections will be made. The firm will also be placed on the FDA schedule for another inspection to verify that the changes have been made.

If the changes have not been made in a reasonable time period, then a Warning Letter may be issued. This is a stronger indication of the severity of the situation. While it is prudent to respond to a 483, it is imperative to respond to a Warning Letter within 15 days.

If the firm is still not compliant then an Injunction may be requested and issued. In the case of a Consent Decree, the firm is being told by the court that they "[author's words] are not good enough to make a quality product; however, if that product is needed in the market, they must hire outside experts – consultants – to work at the firm and verify each batch of the product, until the FDA agrees that the company is able to produce the products of the correct Identity, Strength, Quality, and Purity themselves." Consent Decrees remain in place until the firm has made the necessary changes and shown that it is capable of producing the quality product(s) in compliance with the regulations. This is often for 1, 2, or 3 years, since many changes must be made and cannot be implemented in a shorter period of time. Invariably, management changes are needed. Consent Decrees are both embarrassing and costly.

If all else fails, the firm can be shut down completely.

The content above describes the purpose and nature of Food and Drug Administration Inspections.

3. Documents Reviewed by JJF

A white loose leaf binder containing 25 tabbed sections was sent to James Farley by The Miller Firm. The binder was labeled "Digitek Documents." The package also contained a letter from Peter A. Miller to James J. Farley dated January 26, 2010. The letter stated that the documents were enclosed. Each tabbed section contained one, or several, documents, related to Actavis Totowa at various sites in the area of Totowa, New Jersey. Other company names mentioned in the set of documents are Mylan Laboratories, Bertek Pharmaceuticals, and Amide Pharmaceuticals.

Additional white loose leaf binders were subsequently received. One was labeled "Supplemental Documents for Digitek Expert James Farley." The last white binder received was labeled. "Supplemental Documents for Digitek Expert James Farley (2)" and had tabbed sections A and B, each of which contained several documents.

The sets of documents contain, among other things, FDA 483s, Warning Letters, Actavis responses, a Consent Decree, and parts of a batch record of Batch 70924A1. The complete list is contained in the section below, "Documents Reviewed by James J. Farley." There are some points to be made regarding the documents. These points are listed as "Notes" before the actual list of documents.

Note 1: Dates of inspections listed by me are the dates the inspections were concluded. They spanned several days that were not necessarily consecutive. Therefore, a single date is used here. In the documents, the range of dates of an inspection is given.

Note 2: There are some cases of seeming duplications of documents. In most of these cases there are different redactions so that, while the titles of the documents are identical, the readable portions are different.

Note 3: The documents in the first big white binder ("Digitek Documents") occupied positions in tabbed sections and are listed as such. Some documents in the various white binders had Plaintiff's Exhibit (PE) numbers while others had no numbers.

Note 4: The date formats are different in different documents, generally in accordance with their formatting in the document that was reviewed.

Note 5: In the "Tab" and "PE" columns the numbers in parentheses ( ) indicate that the document has been listed earlier in the tabulation. There are, in many cases, different redactions of the same document; therefore, all documents, even those with titles that were previously logged in here, were reviewed.

Note 6: Regarding Bates numbers, some documents had them and some did not have them. Of those that had Bates numbers most were legible but some were not legible. The numbers are quoted exactly as on the documents. For example, some began with MYLN and others began with MLYN. Documents are referenced here by binder and tab number, Plaintiff's Exhibit number, and by Bates number, whichever is available to reference any individual document.

Documents Reviewed by James J. Farley

			Big White Binder with Tabbed Sections
Tab	**PE**	**Subject**	**Document**
1		Distributing Agreement	5 August 1999 Mylan/Amide Distributing Agreement [MLYN 000032383 - MLYN 000032445] [63 pages; many numbers illegible]
2		FDA Inspection	Form 483 (Little Falls Facility) 08 Feb 2006 (FOIA Request)
3	68	FDA Inspection	Form 483 (Little Falls Facility) August 10, 2006 (FOIA Request)
4		FDA Warning Letter	15 August 2006 FDA Warning Letter [ACTAV 000028926 - ACTAV 000028928]
5	69	FDA Inspection	17 Nov 2006 Nasrat A. Hakim, Actavis, Response to 8/10/06 Form 483
6		Chronology	Jan 2007 - Mylan PowerPoint - Chronology of Actavis Totowa (formerly Amide) Regulatory Issues [MLYN 000032351 - MLYN 000032359]
7		Quality Systems Improvement Plan (QSIP)	01 Feb 2007 Talbot to FDA
8	25	FDA Warning Letter	01 Feb 2007 Revised Warning Letter [ACTAV 000028242 - ACTAV 000028248] [7 pages; 1 number illegible]
9		Supply Agreement – Mylan Bertek and Amide [sic]	01 Feb 2007 Mylan Primary Manufacturer as per ANDA 6.7(b) [MYLN 000284735]
10		FDA Inspection	05 Sept 2007 483 Little Falls [ACTAV 000028940 ?? - ACTAV 000028943] [4 pages; 2 numbers illegible]
11		FDA Inspection	"Establishment Inspection Report 483" [sic] of 09/05/07
12		Incident Report	Lot 70924 30 Nov 2007 Incident Report [ACTAV 000002757]

13	26	FDA Inspection	483 (Riverview Facility) 20 May 2008 (FOIA Request) [ACTAV 000028225 - ACTAV 000028240]
14		FDA Inspection	"Establishment Inspection Report 48" of 03/18/08
15		FDA Inspection	21 May 2008 Actavis Response to 5/20/2008 FDA 483
16		FDA Inspection	6 June 2008 Actavis Response to 5/20/2008 FDA 483 [ACTAV 0000 ?? - ACTAV 000028824] [5 pages; first number illegible]
17		FDA Inspection	11 June 2008 Actavis Response to 5/20/2008 FDA 483 [ACTAV 001302483 - ACTAV 001302501]
18		FDA Inspection	25 July 2008 Actavis Response to FDA 483
19		FDA Inspection	15 Aug 2008 Actavis Response to 5/20/2008 FDA 483
20		Injunction	US Dept of Justice Complaint for Permanent Injunction
21		Consent Decree	US Dept of Justice Consent Decree of Permanent Injunction
22		Consent Decree	9 Jan 2009 FDA News Release – *FDA Awaits Court's Entry of A Permanent Injunction Against Actavis Totowa, LLC*
23		Timeline	Actavis Totowa LLC Timeline [ACTAV 000309763]
24		Mylan Letter (internal) re: 3rd party manufacturers	03 May 2008 Mylan Quality Agreement Letter
25	16	Deviation Report	Investigation of Deviation Report [various sequential and nonsequential numbers, 67 pages]
			Supplemental Documents White Binder
Tab	**PE**	**Subject**	**Document**
	(26)	FDA Inspection	483 (Riverview Facility) May 20, 2008 [ACTAV 001894428 - ACTAV 001894462]
(2)	79	FDA Inspection	483 (Little Falls Facility) Feb 8, 2006 [ACTAV 0000289 ??] [7 pages; most numbers illegible]

(4)	229	Warning Letter	Douglas Ellsworth, FDA District Director (DD) to Divya Patel Aug 15, 2006 [ACTAV 000923261 - ACTAV 000923264] [4 pages; 1 number illegible]
(3)	68	FDA Inspection	483 (Little Falls Facility) Aug 10, 2006
	90	FDA Inspection	Establishment Inspection Report (EIR) (Little Falls Facility) Aug 10, 2006
	228	FDA Inspection	Letter from Nancy Rolli, FDA Supervisory Inspector to Divya Patel dated Nov 17, 2006 with EIR of October 11, 2006 attached [20 pages; numbers illegible]
(8)	25	Revised Warning Letter	Douglas Ellsworth, FDA District Director (DD) to Divya Patel [ACTAV 000028242 - ACTAV 000028248] [7 pages; 2 numbers illegible]
(10)	50	FDA Inspection	483 (Little Falls Facility) Sept 28, 2007
(11)	158	FDA Inspection	Establishment Inspection Report (EIR) (Little Falls Facility) Sept 28, 2007
	(26)	FDA Inspection	483 (Totowa Facility) May 20, 2008 [ACTAV 000028225 - ACTAV 000028240] [16 pages; 2 numbers cut off but readable]
(14)	91	FDA Inspection	Establishment Inspection Report (EIR) (Totowa Facility) May 20, 2008
	115	Actavis Quality	Mike Adams to Vincent Mancinelli (both of Mylan) dated April 28, 2008 the subject of which is "Discussion with Actavis Quality" [MYLN 000934214]
	106	Actavis internal memo on FDA Little Falls Inspection Closeout	Unsigned. On Actavis letterhead. May 20, 2008 [ACTAV 00054300 ?? - ACTAV 000543004] [4 pages; 1 number illegible]
	221	Actavis Recall Package	Actavis Recall Package for Digitek (Digoxin tablets, USP) 0.125 mg and 0.25 mg. [ACTAV 000028178 - ACTAV 000028222]

	220	Letter – Omega to Actavis	Corporate and Occupational Health Services re: Health Hazard Evaluations of Digoxin tabs 0.125 mg. [ACTAV 000006569] and [ACTAV 000006579 - ACTAV 000006580]
(5)	(69)	Letter – Actavis to FDA	Nasrat Hakim to Andrew Ciaccia, Compliance Officer. Monthly Update.
(20)	82	Complaint for Permanent Injunction	U S Dept of Justice (DOJ) v. Actavis Totowa LLC.
(21)	214	Consent Decree of Permanent Injunction	U S District Court, District of New Jersey. Civil Action No. 08-cv-05656 Hon. Susan D. Wigenton
(6)	233	Chronology of Actavis Regulatory Issues	Chuck Koon, Mylan, to Patricia Latzo, Mylan [MLYN 000032351 - MLYN 000032359]
	234	Chronology of Actavis Regulatory Issues	Chronological Tabulation [MYLN 00001668 ??] [number illegible]
	136	Mylan audit	Report of audit of Actavis. Pinnell and Streater [5 pages; numbers illegible]
	147	Actavis e-mail	Phyllis Lambridis, V P U S Quality & Compliance to Jacob Haroon, then to Jasmine Shah. Contains May 20, 2008 Totowa facility 483 [ACTAV 000500876 - ACTAV 000500892]
	235	Amide's FDA inspectional history	Amide's FDA inspectional history March 23, 1992 – March 31, 2004 Author unknown [ACTAV 001087612 - ?] [10 pages; most numbers illegible]
		Jasmine Shah deposition	Former Actavis U S V P for Regulatory and Medical Affairs

			Supplemental White Binder (2) containing Tab A and Tab B sections
			Tab A section. Responses.
Tab	**PE**	**Subject**	**Document**
		483 Response letter.	483 response, Divya Patel to Douglas Ellsworth dated August 29, 2006 [ACTAV 000511447 - ACTAV 000511481]
		Warning Letter 06-NWJ-15 response.	Response, dated September 6, 2006, to August 15, 2006 Warning Letter 06-NWJ-15, Divya Patel to Sara A. Della Fave at FDA, copy to Douglas Ellsworth at FDA [ACTAV 000028929 - ACTAV 000028933]
		FDA response to D. Patel's Warning Letter 06-NWJ-15 response.	FDA to Divya Patel regarding his responses to the August 15, 2006 Warning Letter 06-NWJ-15 [ACTAV 00002884 ?? - ACTAV 000028849] [4 pages; 2 numbers illegible]
		483 Response letter.	Response, dated June 6, 2008 to the 483 dated May 21, 2008, Phyllis Lambridis, Actavis' V P U S Quality Assurance to Douglas Ellsworth at FDA
		483 Response letter.	Letter dated May 21, 2008, from Sigudur Oli Olafsson, Deputy CEO Actavis Group to Douglas Ellsworth, District Director, FDA.
		483 Response letter.	Letter dated June 11, 2008, from Sigudur Oli Olafsson, Deputy CEO Actavis Group to Douglas Ellsworth District Director, FDA. Signed by Phyllis Lambridis for Sigurdur Oli Olafsson.
		483 Response letter.	Letter dated June 20, 2008, from Sigudur Oli Olafsson, Deputy CEO Actavis Group to Douglas Ellsworth, District Director, FDA. [ACTAV 00002827 ??] [19 pages; numbers illegible] and [ACTAV 000296189 - ACTAV 000296190]
		483 Response letter.	Letter dated July 25, 2008, from Sigudur Oli Olafsson, Deputy CEO Actavis Group to Diana Amador-Toro, Acting District Director, FDA. Signed by Phyllis Lambridis for Sigurdur Oli Olafsson.

		483 Response letter. Response to follow-up questions on 483 responses.	Letter dated August 15, 2008, from Anthony J. Delicato, Director, Quality Assurance, Actavis Group to Ms. Sarah A. Della Fave, Compliance Officer, FDA.
			Tab B section. OOS Documents
Tab	**PE**	**Subject**	**Document**
	241	Out - of - Specification (OOS) Digoxin Tablets 0.25 [mg?]	Letter dated June 8, 2004, from Jasmine Shah, Amide, to Amin Nanji at Rite Aid Pharmacy. Subject is Thick Digoxin Tablets, 0.25 mg. [ACTAV 001316391]
	128	Out - of - Specification (OOS) Digoxin Tablets 0.25 [mg?]	Amide Investigation Report with initiation date 7/9/04. Subject is Thick Digoxin Tablets. [ACTAV 001375829 - ACTAV 001375833]
	242	Out - of - Specification (OOS) Digoxin Tablets 0.25 [mg?]	Letter dated July 13, 2004, from Jasmine Shah, Amide, to Amin Nanji at Rite Aid Pharmacy. Subject is Thick Digoxin Tablets. [ACTAV 001316392]
	261	Content Unifomity of a batch of Digoxin Tablets 0.125 mg.	Memo dated January 13, 2007, from Daniel Bitler, Actavis to Investigation OOSN06-014. Subject is "...Product Disposition of Batch 60992A." [ACTAV 000023139 - ACTAV 000023147]
	133	Status Report [on batch record reviews?]	e-mail dated September 27, 2007, from Scott Talbot, Actavis to Jasmine Shah and others. Subject: Status Report. [ACTAV 001420145 - ACTAV 001420151]
	44	Incident Report	Incident Report. Control number 70924A1, prepared by Packaging Manager (Delip Joshi?). Subject is two Digoxin tablets 0.125 mg were found with approximately double thickness. [ACTAV 000002757]
	172	Chromatographic and release data.	e-mail on March 19, 2008 from Jisheng Zhu to Elina Novikov, in response to her e-mail. [ACTAV 000174387]

	143	Digitek batches on HOLD	e-mail on April 2, 2008 from Suzanna Wolfe to Janet Kinsley, both of Mylan, in response to her e-mail. [MYLN 000032816 - MYLN 000032817]
	217	List of investigations by product	e-mail dated April 15, 2008, from Misbah Sherwani, Actavis to "blank field". Subject: List by Product [ACTAV 000299883] [7 pages; most numbers illegible]
	159	Blend failure investigation	Blend Failure Investigation. Printed names are Leroy Lundner and Scott Talbot. No signatures or dates. [ACTAV 000165623 - ACTAV 000165630]
	63	High or low weight tablets. "Digitek 0.125 mg. lot # 80228A1"	Series of e-mails on February 25, 2009 from Lisa Bennet, Paul Galea, and Danielle Comrie – individually.
		"double thick tablet"	e-mail on April 30, 2008 from Jennifer Urso of Pharmacy Services Golden Living Clinical Services to Jill Abraham at Mylan Labs – individually. [MYLN 000932683]
			White Binder labeled "Depositions of Phyllis A. Lambridis and Wanda Eng
Tab	**PE**	**Subject**	**Document**
		Phyllis A. Lambridis deposition	Phyllis A. Lambridis deposition of January 18, 2010
		Wanda Eng deposition	Wanda Eng deposition of January 28, 2010
			White Binder labeled "Deposition of Phyllis A. Lambridis, also Plantiff's Exhibits 105 through 124
Tab	**PE**	**Subject**	**Document**
		Phyllis A. Lambridis deposition	Phyllis A. Lambridis deposition of January 18, 2010
	105	Phyllis Lambridis's Career Summary	Phyllis Lambridis's Career Summary

	(106)	Actavis Internal Memo on FDA Little Falls Inspection Closeout	FDA Little Falls Inspection Closeout An Actavis Document, dated May 20, 2008 [ACTAV 00054300 ?? - ACTAV 000543004] [4 pages; 1 number illegible]
	107	Digoxin	e-mail Phyllis Lambridis to Chris Young dated April 9, 2008 [ACTAV 000292438 - ACTAV 000292439]
	108	Actavis Totowa Corrective Action Plan	Actavis Totowa Corrective Action Plan, Status Report dated August 28, 2008 [ACTAV 000918567 - ACTAV 000918577]
	109	Product list	e-mail Divya Patel to Kevin Anderson dated April 11, 2008 [ACTAV 00047589 ??]
	110	Organization Charts - Actavis	Organization Charts - Actavis (undated) [ACTAV 000542861 - ACTAV 000542865]
	111	Offer to help	e-mail Tony Castellazzo to Phyllis Lambridis March 17, 2008 [ACTAV 000609594 - ACTAV 000609596]
	112	Totowa FDA Audit	Totowa FDA Audit - set of charts and tables [ACTAV 001863647 - ACTAV 001863683]
	113	Actavis – Digitek drug recall letter	Actavis – Digitek drug recall letter – Phyllis Lambridis – April 24, 2008 [ACTAV 000526961 - ACTAV 000526969]
	114	Stopping Digoxin Production	e-mail Phyllis Lambridis to Bitler, Anderson, and others dated April 30, 2008 [ACTAV 000142150 - ACTAV 000142151]
	(115)	Halted production at Totowa facility	Memo Mike Adams to Vincent Mancinelli dated April 28, 2008 [ACTAV 000934214]
	116	Assessment meetings	e-mail Anthony Castellazzo to many people, dated August 14, 2008 Subject is Assessment Meetings [ACTAV 0003024 ??]

	117	"GMP Storm Cloud"	Phyllis Lambridis to Misbah Sherwani, dated August 13, 2008 Subject is GMP Storm Cloud [ACTAV 000527229 - ACTAV 000527231]
	118	Various quality issues	e-mail Phyllis Lambridis to Tony Delicato dated September 16, 2008 [ACTAV 001267772]
	119	Deviations and CAPA report	November 2008 Monthly Deviations and CAPA Data. [ACTAV 000309296 - ACTAV 000309305]
	120	Actavis – Digitek drug recall letter	Actavis – Digitek drug recall letter – Phyllis Lambridis – April 28, 2008 [UDLL 000004006 - UDLL 000004008]
	121	Completely redacted, unidentified document	Two completely redacted pages of an unidentified document [ACTAV 001472833 - ACTAV 001472834]
	122	Tabulation of investigations.	Set of tables and charts of investigations [ACTAV 001423183 - ACTAV 001423220]
	123	FDA refusal to permit Changes Being Effected in Zero Days.	e-mail from Rahana Hussain to several persons dated April 14, 2008 Subject is FDA Communications [ACTAV 001423939 - ACTAV 001423942]
	124	Defines adulterated drugs	Section of the U S Code 351 Adulterated Drugs and Devices. TITLE 21 > CHAPTER 9 > SUBCHAPTER V > Part A > § 351
			This is the end of the Document Section.

4. Additional Reference Sources

- The United States Food, Drug, and Cosmetic Act
- Title 21 of The Code of Federal Regulations, primarily parts 211 (cited 21CFR211) and 7, and other parts
- *The Physician's Desk Reference, PDR*, 63rd edition, Year 2009
- *The Merck Index*
- The FDA Investigations Operations Manual (IOM)

- The FDA Compliance Program Guidance Manual, 7356.002
- The FDA Guidance for Industry - Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, October 2006
- The FDA Guide to Inspections of Dosage Form Drug Manufacturer's CGMPRs (Current Good Manufacturing Procedure Regulations), October 1993.

5. Comments

While the reviews of all the documents listed in the table above provided for the evaluation of the regulatory status of Actavis Totawa, the comments below, some with excerpts, will provide examples of why the conclusions were not only formulated but were readily apparent.

A- Undated and unsigned correspondence from Actavis relating to the "Little Falls Inspection Closeout – May 20, 2008" (Plaintiff's #106) contains such comments as "...from a Quality Systems standpoint there was 'Total Failure'..." and "... there is a need for... Improved Infrastructure, Personnel, and a Philosophical Shift" and "Robert Wessman [Executive Chairman Actavis U S] agreed that the Little Falls site needs new systems and experienced personnel" and "...48 products with no impurity profile." To have a "total failure" such as this indicates that there is no product of this company at that location that can be relied upon to be of the proper "Identity, Strength, Quality, and Purity" acceptable to the FDA as being safe for the consumer.

B- Quoting from page 8 of the Complaint for Permanent Injunction which is in Tab 20, (also as Plaintiff's #82), "...FDA conducted another inspection of Actavis Totowa's Little Falls facility and observed numerous CGMP deficiencies that were the same or similar to observations from the previous inspection...." This leads any responsible person to ask the question: "Why didn't they fix what was broken?"

C- The United States, through the Consent Decree (Plaintiff's #214), instructs Actavis Totowa (page 6, Section 4 C) to engage the services of an independent expert – the GMP Expert – to determine whether the methods, facilities, and controls conform to GMPs. This is usually a consulting firm and many consultants are required to function as a team to bring the company into compliance. This is done because it is recognized that the company is not capable of bringing itself into compliance. It is done when a product is needed by the public but the firm can't produce the necessary quality on its own, and therefore, a third party (a consulting firm) guides the company in the manufacturing and testing of its products. It is embarrassing and costly.

D- Regarding Product Recalls - Recalls are actions taken by a firm to remove a product from the market. Recalls may be conducted on a firm's own initiative, by FDA request, or by FDA order under statutory authority. When done at the request of the FDA such a recall is still considered voluntary. However, if the firm does not recall the product as the FDA requested it to do, the FDA will usually, as a next step to protect the consumer, employ the actions of Seizure or Injunction against the firm. The FDA does not recall products. It requests the manufacturer to recall the products. The manufacturer or distributor does this and therefore it can be called a

voluntary recall. Additionally, a Class I recall is employed in a situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death. Class II and Class III recalls are important yet are employed where the probability of serious adverse health consequences is remote. Class I was employed in this case.

E- Fact versus Opinion. The FDA 483 contains a list of observations which are violations of the regulations. Inspectors and scientists are trained to list only facts and not opinions on the document.

A fact is listed and then examples are provided. No opinions are to be on a 483. (The underlines in this section are by James Farley)

The FDA Investigations Operations Manual (IOM) states, in **section 5.2.3.2, Reportable Observations**, "You should cite factual observations of significant deviations from the FD&C Act…"

The FDA Investigations Operations Manual (IOM) states, in **section 5.2.3.2.1, Adulteration Observations**, "Include specific factual observations…"

The FDA Investigations Operations Manual (IOM) states, in **section 5.2.3.2.2, Other Observations**, "You may include other factual observations of significant deviations from the FD&C Act…"

The FDA Investigations Operations Manual (IOM) states, in **section 5.2.3.3, Non-Reportable Observations**, "Do not report opinions, conclusions, or characterize conditions as 'violative.' The determination of whether any condition is violative is an agency decision made after considering all circumstances, facts and evidence."

F- In the Federal Food, Drug, and Cosmetic Act, specifically, **Sec. 501. [21 USC §351] Adulterated Drugs and Devices**, it is stated that "A drug or device shall be deemed to be adulterated…if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess…." Therefore, since the Actavis facility was determined to be in violation of (not in compliance with) good manufacturing practices, GMPs, the drugs that were produced were adulterated. Additionally, since the non-compliance problem was systemic, all products, including Digitek, were adulterated.

G- Blend Uniformity. In the FDA 483 dated May 20, 2008 (Plaintiff's Exhibit #26) Observation 4 mentions blend uniformity problems. 4a mentions out-of-specification results for blend uniformity for Digoxin Tablets 0.125 mg. 4c mentions "…approximately [redacted] products were 'temporarily discontinued' due to blend uniformity and/or content uniformity issues…." Blend uniformity refers to the blended material before pressing into tablet form. Content uniformity means the uniformity of individual tablets, that is, the uniformity of the amount of active ingredient measured tablet to tablet. This is extremely important with Digoxin since the

active ingredient is theoretically present to the extent of 0.125 milligram (mg) in a tablet weighing 105.000 milligrams. That is 1.2 parts active ingredient per 1000 parts total tablet weight. Proper blending is very important here. In comparison, a 200 mg strength Advil (ibuprofen) tablet contains 200.0 mgs active ingredient per total tablet weight of 528.0 mgs which is 378 parts active ingredient per 1000 parts total tablet weight. Another example is the 10 mg strength Lipitor (Atorvastatin Calcium) which contains 10.0 mgs active ingredient per total tablet weight of 152.0 mgs. This is 65 parts active ingredient per 1000 parts total tablet weight.

6. Conclusions

My conclusions are based on my knowledge and experience of the pharmaceutical industry, being employed in the industry being regulated, working at the FDA, which is the regulator, and the last 14 years as a pharmaceutical and FDA regulatory consultant. My experience is detailed at the beginning of this report as **"1. Qualifications"**.

Based on the review of the documents listed in this report I conclude that Actavis had essentially no quality control over the products it produced and shipped. There are violations in the areas of Adverse Event reporting, Out - of - Specification (OOS) investigations, Deviation investigations, the Corrective Action; Preventive Action (CAPA) program, and various GMP areas. All of these are shown to recur thereby indicating that no corrective actions were made.

There are many Good Manufacturing Practice (GMP) infractions that recur. This should not be the case with any pharmaceutical firm. Once an infraction is noted as an "Observation" on any FDA form 483 it should be addressed and corrected. To not correct an infraction is to either not care or be unable to comply, or both. Quoting from the Complaint for Permanent Injunction which is in Tab 20, "...FDA conducted another inspection of Actavis Totowa's Little Falls facility and observed numerous CGMP deficiencies that were the same or similar to observations from the previous inspection...."

To be under a Consent Decree for more that 10 consecutive years is an indication of continuing serious problems with FDA regulations. The history of the company from Amide through Actavis Totowa is a series of FDA regulatory problems from "483s" to Warning Letters to the longstanding Consent Decree, all of which indicate varying degrees of non-compliance with FDA regulations and show the inability to produce products that meet the standards necessary to ensure safety for the consumer.

The problems at Actavis are systemic. That is, they are part of the actual operation of the company in its attitude and in its production of drugs for consumers. When such problems are systemic they are based in the management of the company. Changes are needed by or within Actavis management structure to correct the situation and bring the company into compliance with FDA regulations, and to ensure that safe, quality products are manufactured. Since the non-compliance problem was systemic, all products, including Digitek, were adulterated as defined in Section 501 of the Food, Drug, and Cosmetic Act.

Patients have no assurance of the proper quality of the Actavis products since many were produced under non-compliant conditions in violation of FDA regulations.

James J Farley June 14, 2010

James J. Farley
Consultant - Smart Consulting Group
June 14, 2010

SpyGlass Group, Inc.

2 Spyglass Ct.

Annandale, NJ 08801

Expert Opinion Report

Quality Assurance & FDA Compliance

Actavis Inc.

Makers of Digitek

By

Mark G. Kenny

15 – June– 2010

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Expert Qualifications

The SpyGlass Group, Inc[1]. was contacted by the law firm Motley-Rice, seeking an expert in Quality Assurance and current Good Manufacturing Practice (cGMP)[2] to provide expert opinion in regard to a legal action against Actavis Inc. (formerly known as Amide), a manufacturer of drug products.

I have been engaged by Motley-Rice to prepare an expert report, participate in a legal deposition and testify as an expert witness in a trial. My expert opinion is based upon on over 35 years experience in:

- Running the Quality Assurance and Compliance Programs for multiple drug, medical device, diagnostics and consumer products manufacturing companies (from small start-up to large multinational companies)
- Objectively and fairly auditing hundreds of domestic and international medical products companies engaged in the development , manufacture and distribution of products regulated by the FDA
- Determining the potential adverse effects that noncompliance has on the product quality and the customer's trust in the product
- Reporting to senior management, risks associated with faulty control systems
- Understanding industry standards commonly used to comply to cGMP
- Reviewing quality records for the purpose of identifying potential violations to cGMP
- Investigating root cause of noncompliance and recommending reliable fix
- Creating effective corrective action programs for many companies in serious violation of cGMP, subsequently eliminating public health risks
- High level consulting for major medical industry companies

The complete CV for Mark G. Kenny is included as *Appendix A – Mark G. Kenny CV*. The following summarizes my related assignments:

- SpyGlass Group Managing Director (6 years)
- Corporate (Regional) Quality Assurance Director for Johnson & Johnson (J&J) Corporate (Headquarters) (8 years)
- Executive Director of Quality Assurance and Management Board Member for Direct Access Diagnostics (J&J) – Home diagnostic products, including home HIV test (3 years)

[1] Quality & Compliance Consulting Group – website: www.spyglassgroupinc.com
[2] 21 CFR Part 210 and 21 CFR Part 211 Current Good Manufacturing Practice for Manufacturing, Processing, Packing, or Holding of Drugs and Finished Pharmaceuticals

- Executive Director of Quality Assurance and Management Board Member of Advanced Care Products (J&J) – Monistat and other OTC products (3 years)
- Director of Quality Assurance and Labs for IOLAB (J&J) – Intraocular Lenses, Electro-Mechanical Devices for Ocular Surgery (3 years)
- Director of Quality Assurance Compliance for Ortho Pharmaceutical Inc (J&J) – Oral Contraceptives, dermatological drug products, monoclonal antibody drug products, antifungal drug products (3 years)
- Director of Quality Assurance (External Manufacturing) Johnson & Johnson Consumer and Healthcare Products – women's healthcare drug products, dermatological products, wound healing products, medical device products (5 years)
- Validation & Pilot Project Engineer for Ethicon Inc. – wound closure devices (4 years)

Achievements include:

- Authored Multiple J&J Corporate Policies – including sterilization
- Partnered with the FDA and lead the GMP compliance effort & late stage development team for the First FDA Approved Home HIV Test
- Lead GMP Compliance for First FDA Approved Monoclonal Antibody Therapeutic Product
- Lead Assessor for Multiple J&J Acquisitions
- Reversal of negative GMP Compliance trends for multiple companies
- Lead auditor on many high profile compliance situations
- Developed hundreds of Quality Assurance and System Procedures
- Developed multiple Master Validation Plans and Master Compliance Plans
- Johnson & Johnson lead representative on HIMA (Health Industry's Manufacturing Association) cGMP Committee and CHPA (Consumer Healthcare Products Association: formerly called Non-Prescription Drug Manufacturer's Association) on the Stability Testing Committee
- Authored Multiple J&J Corporate Worldwide Guidelines
- Lead the GMP compliance preparation for multiple companies
- During FDA Inspections, defended the GMP Compliance Program for multiple companies
- Throughout J&J domestic companies, became the second Quality Assurance & Compliance head to be appointed to a company's Management Board
- Lead two different company's Quality & Compliance Programs from being rated "worst" to "best"
- Established a consulting company comprised of former senior executives in Medical Products Technology, Quality Assurance, Compliance, Operations and Regulatory Affairs
- Awarded seven (7) Johnson & Johnson Leadership Awards for GMP and Quality achievements – this is J&J's highest personal award

Introduction

The SpyGlass Group, Inc. has determined that Actavis/Amide (hereafter referred to Actavis) was not complying with the FDA legal requirements for current Good Manufacturing Practice (cGMP or GMP) for at least the period of time, starting in 12/1/2004[3] and ending with their Permanent Injunction of Nov. 14, 2008[4]. Because of the serious violations of GMP, for this period of time, the production, control and quality processes for Digitek were not able to consistently and reliably manufacture products that meet legal requirements. During this period of time, the records demonstrate that Actavis released product that did not meet product specification and as such were adulterated[5].

Their troubled past included a 1992 FDA Consent Decree. Then there was some period of time (1993 through the 1st Quarter of 2004) when FDA records indicate that the operations were GMP compliant. There were several FDA adverse inspectional findings notices (commonly called FDA Form 483 or just 483) issued over this period of time; however, Actavis/Amide corrective action appeared to have satisfied the FDA's concerns. Then for a period of six (6) years, beginning in 2004 until their 2009 Permanent Injunction, there appears to have been a significant breakdown in their Quality Systems and overall compliance to GMP. As a result of multiple FDA site inspections over this six (6) year period, Actavis was issued multiple FDA adverse finding reports. As a result of not taking swift and effective corrective action to the FDA 483s, the FDA escalated their public concern by issuing numerous FDA Warning Letters (*See section A Primer on cGMP FDA Regulations & Important Quality Assurance Concepts* for more information on Warning Letters.) Actavis did not effectively correct the deficiencies identified in the FDA mandates. After being given every opportunity to correct their deficiencies, through the legal process a Permanent Injunction was served and Actavis stopped manufacturing and release drug products from the affected sites. This type of severe legal action on a United States drug company is exceedingly rare. My review of the evidence confirms the good judgment of the FDA.

A detailed evaluation of the cGMP Compliance history of Actavis was performed by the Spyglass Group for the period of 2006 – 2008[6]. The FDA conducted five (5) inspections over this period that resulted in over 40 significant observations and two (2) Warning letters and a final Consent Decree for Permanent Injunction.

In this Expert Report, the SpyGlass Group has classified the FDA observations into five (5) system categories:

1. Quality System
2. Facilities & Equipment Systems

[3] FDA Form 483, Issued to Divya C. Patel (President), District FDA Office in Parsippany - NJ, 12/1/042004
[4] Plaintiff's Exhibit #82, Complaint of Permanent Injunction, 11/14/08
[5] Plaintiff's Exhibit #124 – Definition of an adulterated drug, US doc. 351.
[6] Appendix D Summary of FDA Observations & Events

3. Production System
4. Laboratory & Control System
5. Regulatory Requirements

Beginning in 2004, Actavis produced products using processes and control systems that were shown to be unreliable. To illustrate this conclusion, in only a two (2) year period (primarily 2007-2008) there were over:

- 300 Out of Specification (OOS) incidences (2007-2008)
- 300 Formal Investigations (2007-2008)
- 200 Deviations (2007-2008 -over a 12 month period)
- 20 Rejected Batches (2006-2007 – 12 month period)

The number and type of issues indicate that the company operated in a state of nonconformance for an extended period of time.

Additionally, a review of some of the investigations associated with Digitek identified significant issues that are specific to many batches, including double thick tablets.

Management at Actavis was aware of this and other GMP issues but failed to adequately correct the problem. When comparing 2007 to 2008 for Laboratory OOS, there was no improvement in numbers. When comparing 2007 to 2008 for Investigations, the number doubled for 2008. They performed inadequate investigations into the nonconformances; therefore, they were unable to implement sustainable improvements.

The detailed analysis of the FDA findings determined that each of these systems had numerous observations. There was consistent inadequate corrective action; therefore, there was a pattern of repeat observations. Critical systems that control the Quality of the product were substantially and consistently out of compliance and operating in a high risk environment. There was no apparent attempt to mitigate the product quality risks through extra testing, inspection, etc.

My independent findings have confirmed the FDA issues. Additionally, many more issues were identified that demonstrated that Actavis was critically noncompliant with GMP regulations and released product that did not meet GMP. The product manufactured during this period of time was adulterated (See Page 12 for description of adulterated drug.)

It is my opinion to a reasonable degree of certainty and based upon my experience and qualifications and after reviewing hundreds of pages of evidence that Actavis management's actions or lack thereof, demonstrate that legal compliance with Federal Regulations as stated in the GMP section of the Code of Federal Regulations was not one of their business priorities. Over at least a six (6) year period, Actavis failed to meet legal and patient obligations.

Work Plan

Approach

- Review documented evidence applicable to the scope of the assignment
- Prepare an expert witness report that documents my findings
- Participate in future legal proceedings which may include deposition(s) and a trial process

Quality and Control Systems

- To determine whether or not Actavis was operating within cGMP FDA regulations

Product Quality

- To determine whether or not Digitek (digoxin) tablets made over the period of 2003 to 2008 met the requirements for identity, strength, quality that they purport to have and were fit to be released for sale
- To determine whether or not Actavis had or had not released adulterated product

A Primer on cGMP FDA Regulations & Important Quality Assurance Concepts

What is Drug c GMP?

Current Good Manufacturing Practices (cGMP or more commonly called GMP) is a law that was established in the Code of Federal Regulations. It represents the minimum requirements in the Drug Industry for producing a product that meets all specific requirements for identity, strength, quality, and purity. The law was originally drafted for comment by the FDA using industry acknowledged experts. Industry experts then commented on the content of the draft proposed regulation and in an iterative process, a law was established that outlines the requirements for every drug manufacturer to follow. It has been continually improved (via the same methodology, i.e. industry participation) since its approval. My opinion (which is shared by most industry Quality & Compliance leaders) is that it is a well designed document and of great help in ensuring that patients and customers receive 100% safe and effective drug products. In fact, most Quality & Compliance leaders place GMP in business terms; frequently refer to GMP as "good business practices." Likewise, it is my experience that the FDA understands the business and fairly and impartially uses a heavy-hand only when they fear public safety. In these high-risk situations, they continually escalate their concerns until all public risks are resolved.

Why is GMP Important?

It is important to understand that the term "Good" is somewhat misleading, GMP is the legal minimum and it is not optional. My opinion (which is shared by most industry Quality & Compliance leaders) is that significant breakdowns of the Quality and Control Systems (established in this regulation) will inevitably result in serious product quality risks; more specifically, "bad product" being released to the American public.

Why is the FDA Requirement of Investigating and Corrective Action So Important?

All of the controls established in the GMP Regulation are important; however, some are more important than others. The concept of Corrective Action and Preventive Action (CAPA) is critical.
When errors (referred to as nonconformances) are discovered in any of the Product Quality and/or Control System, by law, industry must investigate the issue. This is common sense to most people, i.e. when you find a problem you need to understand the seriousness of the problem and resolve the situation accordingly. Some nonconformances are important but not urgent. Other nonconformances require immediate investigation, including notifying top management. This practice is somewhat similar to the triage procedure used in a hospital emergency room. For example, if manufacturing equipment were to produce products that had cosmetic issues (e.g. slight crooked printing) of the carton lot number; this is important

but not necessarily high risk. The operator has the authority to make an immediate adjustment on the equipment and (with Quality Assurance oversight) inspect the product made, determine when the problem occurred and potentially cull out the defective cases for immediate reinsertion and rework. This type of occurrence would generally not require the immediate notification to top management. On the other hand, if defective tablets (for example double thick) were being discovered at any point in the manufacturing process, immediate actions would result. This is a highly disciplined procedure. It is likely that many of the following actions would be performed;

A. The production line would be stopped and not restarted until a complete investigation was performed (in accordance to a detailed control procedure).
B. This category of defect, i.e. oversized or potentially mixed tablets, creates the highest order of concern for the company. Any suspected suboptimal control system that could result in this type of defect is what keeps Quality Assurance Directors up all night.
C. The Manager of Quality Assurance and Manufacturing would be notified immediately
D. A formal and documented investigation would begin (in accordance to another detailed control procedure)
E. Based upon the preliminary investigation, that lot number would be placed on hold and segregated, identifying the product as potentially defective. Additionally, the batch would be identified in the computer inventory control system as on Hold or Quarantined, thus eliminating any chance for the premature release of the potentially defective product. Classifying the product lot as "On Hold" and later reclassifying a product lot as "Accepted" is a key control step. Quality Assurance is the only one that has the electronic "key" to change these product lot classifications. Unless a worker purposely mishandles defective product, it is almost impossible, in current computer inventory control systems, to generate the necessary paperwork to release a batch for sale.
F. A full-scaled documented investigation would follow, ascertaining the specific (root) cause of the nonconformance. The investigation would extend into many of the control systems within the company, far beyond some of the obvious potential causes. The investigation would also be extended to other batches. All potential sources would be systematically investigated to ensure that the problem is not more widespread. As part of the investigation, a determination would be made as to the acceptability of the batch.
G. After the documented investigation has determined the root cause, a specific documented corrective action program would be designed and deployed.
H. A Material Review Board (or equivalent) would meet to discuss the adequacy of the investigation and appropriate next steps.
I. If it is determined to be a risky practice that cannot be quickly corrected then the line would be stopped indefinitely until the risk is eliminated.
J. Depending upon the situation, the production line would be revalidated after the corrective action is complete.
K. Ultimately, QA will decide the outcome. Release of product is not a democratic process.
L. The product would have been destroyed.

What are the Results of Not Following GMP?

There are many potential outcomes, all are adverse. The following identifies a few of these adverse outcomes:

A. FDA Issues - FDA inspections have a reasonable probability to discover the lack of GMP Compliance when problems are more widespread. It is important to understand that no matter how long the FDA spends at the site, they do not have the capability to identify all of the problems. During an inspection, they determine the seriousness of the company's practices and determine the reporting method. When there are issues then the FDA reports the observations using a form – FDA Form 483. Should the situation warrant it, the FDA will continue to escalate their actions from an FDA Form 483 notification to more severe notifications, including: Warning Letter(s), Consent Decree, or worse, including the Permanent Injunction. A Warning Letter[7] is a communication to the firm that has been reviewed within several levels of the FDA, including the district office and the office of compliance at FDA's headquarters. The Warning Letter generally states that the firm has made products that are adulterated, violating the Food, Drug, and Cosmetic Act and that the firm has a very limited amount of time to address the problem(s) before the FDA takes further regulatory action against the firm, the adulterated product, and responsible individuals. Permanent Injunction is highly rare and represents the FDA's highest order of concern. Manufacturing Problems – GMP describes fundamental controls that are necessary to be in business. Most of the top companies in the world (regardless of product category) practice these principles and deploy them exceedingly well. Those companies that do not are likely to have significant lapses in sustaining these procedures and are doomed to have product recalls. Companies that experience GMP problems are continually "fighting fires" and are constantly being faced with nonconforming product and nonconforming practices.

B. Product Quality – Product quality will always suffer when GMP is not established. The worse the systems, the worse the problems. Each product defect (originating with complaints, production line, packaging line, etc.) needs to be formally investigated. When a company is constantly fighting these types of fires, there are never enough people to manage the fires. The result is that the problems are ignored or the investigations are superficial, having little chance to determine the root cause and less chance to implement an effective and sustainable corrective action. The lack of effective control systems is the common root cause of almost all product defects. The lack of effective control systems will result in the release of product that does not meet specification, adulterated and are unfit for human use. When this type of product is discovered or the quality is suspect, a responsible company will Recall the product. If the company does not recall unsafe product, the FDA can legally seize all affected product.

[7] http://www.cgmp.com/warningLetter.htm

What are Some of the Critical Systems & Controls in Drug Manufacturing?

Batch History Record: This is a compilation of all of the vital records and results that provide evidence that the production lot/batch was manufactured and tested in accordance to approved procedures, test methods and specifications. It is also evidence that a batch complies with any FDA submissions. It is a stand-alone document, which means that it should be understood by any experienced reviewer without any significant explanations. It must be complete. The document must include the records previously mentioned plus any exceptions. Exceptions would include issues that were encountered during the manufacturing or testing of a batch. For example the following documentation is required to be in the batch records: out of specification reports, CAPA reports, rework or salvage records, etc. The final control step, before the product is released to market, is the independent Quality Assurance review. This person's responsibility is to review the records of the batch and ensure that it meets specification and was produced and tested in accordance with approved procedures. Quality Assurance then certifies in writing that the product was manufactured and tested in accordance to the approved procedures and the test results meet all specifications.

Out of Specification Test Result (OOS): If a lab analyst performs a test and discovers out of specification results, then the analyst must follow a strict procedure which involves a formal and documented investigation. The initial first results cannot be automatically disregarded. This FDA required procedure has built in controls to ensure that the final test results are valid. An OOS is a significant occurrence that requires critical thinking and investigation to properly resolve. The documentation associated with the event must be carefully documented in accordance to the procedures. Failure to follow the OOS procedure will yield results that may be incorrect, ultimately allowing unacceptable product to be released to the market.

Nonconformances: When manufacturing or Quality assurance action does not meet the approved procedure then a nonconformance occurs. When a test is performed and the results do not meet the specifications and/or the documented requirements, then a nonconformance occurs. All nonconformances are required by law to be investigated and handled in accordance to approved procedures to resolve the problem.

Good Documentation Practice: This is an informal term for highly formalized controls that are included in the GMP. The following highlights some of the more common sense aspects of good documentation practice. All recorded information must be clear, legible and understandable. When an error is made by an associate, the error must be handled in accordance to procedure. There will be signed and approved signatures next to every change of results. There is a legal code of ethics stated in the GMP that all information including dated signatures must be honest. All documents requiring approval, e.g. CAPA, must be signed by all of the technical and management associates as required by the procedure. There is no exception to this rule. Any records that are not honest are falsified records. Any unapproved/unsigned and undated documents are not acceptable records and almost unusable. Quality Assurance has the responsibility in all steps of the process (raw material receipt and testing, inprocess inspection and testing, product manufacturing and packaging, finished product testing, etc.) to continually review the records as

production progresses. The final Quality Assurance batch history record review is intended to discover good documentation practice nonconformance and hold the batch until a documented investigation is conducted, again in accordance to approved procedures. This is not a nice to do, it is the law. Although the term Good Documentation Practice is not specifically mentioned in this expert report, it is important to understand and have an appreciation for the rules governing records.

Complaint Handling: Each complaint must be properly investigated in accordance to GMP and other FDA guidance documents. This is a disciplined procedure that requires a series of formal events to take place. These steps are intended to determine the potential seriousness of the complaint. The events associated with an investigation may typically include (but is not limited to):

- Examination and chemical testing of the complaint sample
- Examination and testing of product retain sample(s) (retained product samples are required to be selected from every batch and stored in a controlled manner, intended to help investigations into future problems)
- Review of prior complaints with the specific batch
- Review of prior complaints with this specific product and similar products if there is an issue, it must not be automatically assumed that the problem is only affecting the complaint batch.
- Trend analysis
- Inspection of the Batch Record and other records
- Interviews with manufacturing and Quality Assurance
- Review of studies performed, for example equipment qualification studies, process validation studies
- Review of the adequacy of the current procedures and specifications
- Review of the stability testing results

If the investigation determines that there might be unsafe product in the marketplace, then the investigation must be escalated to top management and a recall decision must be considered. This must be conducted in accordance to procedures and FDA Regulations. Some of the activities and documentation may have to be submitted to the FDA for their review.

Managing Contract Manufacturers

It is common for companies to have their products made under contract by a company that specializes in the manufacturing and testing of drug products. The relationship and responsibilities between both organizations is normally established, in part, within a mutually approved Quality Agreement. The Quality Agreement is formally approved by both parties. The agreement itemizes every critical control system and the corresponding responsibilities. The agreement identifies methods to communicate and approve documentation and product release. The FDA requires that companies have well designed control systems to manage their contractors, including Quality Agreements, in place prior to the production of any products.

The contracting company is required by the FDA to formally qualify (i.e. approve) the contractor based upon objective evidence that the contractor is in full compliance with GMP. Normally a GMP audit is conducted at different stages, for example: initial qualification, periodically thereafter (typically once every year or two) and for cause (i.e. problem related). The GMP audit is a highly structured event. An auditor or a team of auditors spends a minimum of one day reviewing documents and records to ascertain the relative level of GMP compliance (similar to an FDA inspection.) A detailed report is then written that includes: scope of audit, itemized areas covered and exceptional findings. The findings are generally categorized by risk level (e.g. major and minor). A final review meeting is held and the findings are reviewed. The audit report is then sent to the contractor who is required to reply to the audit and indicate their proposed corrective action to every nonconformance to GMP regulations. The next audit would review and verify that the corrective action has been effective. All of the previous activities must be done in conformance to a written procedure.

What is an Adulterated Drug?

A 1962 Amendment to the cGMP provision of the FD & C Act, Section 501 (a) (2) (B) states "A drug…shall be deemed to be adulterated if…the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."

This is an important concept because this FDA Amendment dispels any misconception that adulterated product is limited to out of specification test results of a finished product. The FDA has stated that product is adulterated when the procedures, controls, raw materials, components and/or practices do not comply with GMP. There is a recognition that quality products do not happen by accident. It does not happen by merely testing the product at the end of the manufacturing line. It is the result of a highly disciplined approach to establishing controls and procedures using the minimum standards of the GMP. This concept is built on the premise that quality is built into the product rather than tested into the product.

a. Actavis Corporate Culture & Management

There has been consistent evidence that Actavis Management did not understand the importance of GMP and its direct link to product quality. It appears that their lack of understanding begins at their website[8]. Actavis defines their Manufacturing Practice as based upon GMP which is stated as: "Good Manufacturing Practice (GMP) is a regulatory guideline imposed on all manufacturers of pharmaceuticals…" This statement is not correct because GMP is a Federal Law, not a guideline. This is an important distinction.

It is my opinion to a reasonable degree of certainty that management never displayed an understanding of the legal requirements of GMP. In spite of experiencing significant issues, management never altered their flawed strategy.

The significant issues include:

- FDA Form 483
- FDA Warning Letters
- Alarming number of Quality problems
- Product Recalls
- Breakdowns in their Quality System.

It is my opinion to a reasonable degree of certainty that they were highly resistive to systematic change, appearing sure that minor improvements would resolve all of their issues. This was a flawed strategy; their arrogance resulted in managing a drug company that operated at a high risk level.

This 2008 statement by Jacob Haroon (Actavis Director of Regulatory Affairs at the time of the email) describes the situation quite well: "This is all rather sad. Looks like some very basic GMP knowledge was lacking."[9] Unfortunately, it is the patients that could suffer from this risky situation.

It is my opinion to a reasonable degree of certainty that Corporate and QA management were not knowledgeable of the cGMP. Additionally, there was a lack of understanding of the regulatory approval process since many drug products were made and sold without approved NDA's /ANDA's.[10] The Actavis Senior Director of Compliance and former FDA Director of Investigations for New York State wrote[11] that the potential 483 items could include:

- The Quality Unit failed to do its job
- The Quality Unit has released batches of drug products that failed their specifications

[8] http://www.actavis.com/en/products/manufacturing/good+manufacturing+practice.htm
[9] Plaintiff's Exhibit #147 – Email Subject: Form FDA 483 RV.pdf, Jacob Haroon, 5/27/ 2008
[10] Complaint for Permanent Injunction, Case 2:08-cv-05656-SDW-MCA, Christopher Christie (United States Attorney), Filed 11/14/2008, p 11
[11] Exhibit Plaintiff's #146- Email Subject: Totowa Potential 483 items and comments, Wanda Eng, 4/17/2008

- The Quality Unit failed to adequately conduct deviation investigations in that the root cause was not determined
- Failed to file NDA Field Alerts associated with confirmed stability failures
- Failed to reject products which did not meet in-process and finished product specifications
- The Quality Unit released products for distribution prior to the completion of the deviation investigation
- Continued to manufacture and ship unapproved DESI drug products after receipt of a Warning Letter requesting justification to market products
- Tested product into compliance and discarded the OOS results; using only retest results without adequate justification
- Failed to have adequate stability programs
- Laboratory investigation of OOSs were inadequate
- Actavis' filings submitted to the FDA to widen specifications when a product fails to meet specification
- Many manufacturing processes are invalidated by the high percentage of stability failures
- Actavis produced digoxin tablets with black spots of unproven origin
- Actavis produced digoxin, a toxic product with double, triple and thin tablets: lots were not rejected

The Actavis Senior Director of Compliance and former FDA Director of Investigations for New York State also wrote (in full capital letters) that potential 483 items could include:

- "OUT OF CONTROL"
- "LACK OF RESOURCES"
- "LACK OF EXPERTISE"

The FDA stated in the 2006 Warning Letter[12]:

- "Several of the observed deficiencies were long-standing, and there is no indication of how or why the lack of compliance was not identified by your firm"
- "why it was allowed to continue for such an extended period of time"
- "Does your firm have any insight into this situation"?

Mylan stated[13] in their 2006 visit to Actavis that there was a "shortage of qualified personnel".

Actavis did not respond to the critical FDA observations in the August 2006 FDA 483 in a timely manner. Ten (10) months after the 2006 inspection the following was a status of their corrective action implementation in their Totowa Action Plans[14]:

- 5 not corrected

[12] Plaintiff's Exhibit 229 – Warning Letter, Douglass Ellsworth, August 15, 2006
[13] Mylan Audit, Subject: Final Corrective Action Memo, from R. Pinnell, 1/23/2008
[14] Exhibit Plaintiff's #137 – Totowa Action Plan (August 2006 GMP Inspection Totowa), Not dated - estimated July 2007

- 6 partially corrected

In the same document it states that more than half of the August 2006 observations had not been corrected. This includes FDA's observations:

- Failure of the Quality Unit to fulfill its responsibilities
- Quality Unit failed to assure that lab notebooks include all data generated et al.
- SOPs not always followed
- Master production and control records do not include complete sample and procedures

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Actavis Understanding of the Gravity of the Problems

The FDA required that Actavis respond to each adverse notice (483 and Warning Letter). The Actavis letters to the FDA represented two areas: 1. Areas promised to correct and 2. Areas that were already corrected. In some ways, they can be thought of as promissory notes and certification of corrective action. Actavis repeatedly failed in this regard. They frequently made promises that were not kept and improvements and corrective actions that were not adequate or sustainable. After the submission of Actavis' reply to the FDA, there are abundant examples where their reply is not correct. For example, in the Revised FDA Warning Letter – E. Main St. Little Falls - Dated 2/1/2007[15] in regard to Actavis' disagreements with the FDA position, the FDA stated:

- "Your response provides no assurance that the records and conditions of manufacture and testing of each such lot of drug products released and marketed by our firm will be evaluated to assure that the released drug products have their appropriate, identity, strength, quality, and purity
- "In fact, we do not agree with assertions in your August 29 and 30, 2006 letter that certain of the observations listed on the FDA 483 are not accurate"
- "...we are concerned about the quality of the of drug products that have been released from your facility under the serious lack of cGMP controls found during the inspection."

Lack of Timely Remediation

In the Actavis 5/20/2008 Memo to Senior Management[16] – The Actavis scribe summarized the FDA Inspector's statements: "from a Quality Systems standpoint, there was a Total Failure." Additionally, the scribe documented that the FDA stated:

- Do not fix broken systems – get new systems
- (Need) Improved infrastructure
- Investigations on the (past) 483 still not complete
- Health hazards on recalls are delinquent

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[15] Plaintiff Exhibit #25 – Revised Warning Letter, 2/2007

[16] Exhibit Plaintiff's #106 - Subject: FDA Little Falls Inspection Closeout – May 20, 2008, Garret R. Woolan – Scribe, 5/20/2008

- We (FDA) get very nervous when you tell us that you are releasing product using current Quality Systems
- One (QA) person was signing off in multiple locations on the batch (this occurred on the Digoxin "double tablet" Investigation). Erin (FDA representative) considered this a very important Observation – additional review of this Investigation may have stopped release of the batch)
- It was "premature to be releasing product"
- The FDA is concerned about product still on the market that was made in Little Falls using similar systems that had failed
- That FDA has concern about the 48 products with no impurity profiles
- The tougher issues are - What is the approach to handling product made under these substandard systems?
- The FDA questioned the validity of Actavis' Batch Record Review process because the FDA had found important nonconformances (e.g. black spots) that were not included in the record. A review of an incomplete batch history record provides a false sense of security.

February 2009 - Quality System Improvement Plan (QSIP)[17]

A Quality System Improvement Plan was developed with the aid of consultants. This QSIP was started in the 4th Quarter 2008, three (3) years after the first (in a series) of 483 and Warning letters. Well run firms would have responded immediately after the first 483 in 2006. Furthermore, this would be an alarm that the major systems are not in control and product quality might be adversely affected. These firms would have immediately ordered an intensive internal audit and determined the risk level of each Quality System component. A comprehensive action plan would then be established. In the case of Actavis, it required the hiring of a Quality System consulting firm to begin this evaluation and improvement process (Committee started 11/20/08).

The QSIP identified 201 Observations:

1. Materials Management – 27 Observations
2. Facilities & Equipment – 49 Observations
3. Production Controls - 22 Observations
4. Packaging & Labeling – 15 Observations
5. QC Laboratory – 14 Observations
6. QA – 45 Observations
7. Actavis R&D – 29 Observations

As of February 2009, there were still about 24% open observations, over three (3) years after the 2006 FDA 483.

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[17] ACTAV 000484606 – Quality System Improvement Plan, 2/26/2009

Ineffective Internal Audit Process

The Internal Audit Procedure is designed to provide an independent audit of the company's relative compliance to GMP. It provides management with objective information on GMP compliance. Many of the problems associated with the FDA issues should have been identified through the internal audit procedure and formally communicated to management. This is normally an annual event intended to identify GMP risks and provide evidence that the contractor is in a state of control. It also authorizes the continuance of business as usual (unless critical issues are identified during the audit.)

A review of an internal audit[18] (conducted on 1/24/2008) identified issues, most of which were not critical and were specifically related to work instruction steps in a procedures and associated records. There is no evidence that the auditor identified any of the systemic issues that were later identified by the consultants in the 4th Quarter of 2009. It would not be expected that less intensive audit would find all of these observations; however, many of the fundamental issues should have been identified as requiring improvement, providing a red flag to Actavis management. This aligned with the FDA. In the Warning Letter[19] which stated: "Several of the observed deficiencies were long-standing, and there is no indication of how or why the lack of compliance was not identified by your firm"

Senior Management Top Priority – Not on GMP

In a presentation[20] at a company meeting in February 2006, the Executive Chairman for Actavis presented in a slide show: "How Do We Achieve Success?" This will be achieved by Low Cost and most importantly Speed. There is no mention of GMP or Compliance in this presentation.

Actavis Corporate Culture & Management
SpyGlass Group Summary

It is my opinion to a reasonable degree of certainty that:

- The aforementioned examples indicate the gravity of their situation. The environment created by management within the company fostered noncompliant behavior. The abilities and motivations of management have to be questioned based upon their actions.

- The type and frequency of issues indicate that an effective Quality System was never sustained and their GMP legal obligations were never fulfilled. It is highly disturbing that there was a lack of understanding and urgency to these serious issues even after 16 years of significant FDA actions.

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[18] Plaintiff's #175: M. Patel, Email Subject: Regarding internal cGMP audit, 1/25/2008
[19] Plaintiff Exhibit #25 – Revised Warning Letter, 2/2007
[20] Exhibit Plaintiff's #92 – Presentation at a Feb 2006 Sales Meeting, Not Dated

b. Product Quality & Quality Systems

This section of the report analyzes some of the situations related to Product Quality Nonconformances, Deviations and OOS.

The following highlights some of the major Product Quality issues and the alarming rate of OOS, Investigations and Deviations. Items 1 and 2 are specifically for Digoxin. Subsequent Items are general and for all products.

1. There were multiple incidences of Double Thick and Overweight Digoxin Tablet lots:
   - 3611A - 2004 Complaint Report of Double Thickness Tablet. See detailed analysis that follows
   - 70924A2 – Production Report of a Double Thickness Tablet. See detailed analysis that follows
   - 80202A1) – Bulk tablet lot was released[21] to filling and packaging only later to be placed on Hold due to tablet weight issues. "They indicated that this one is the problem child"[22]
   - 5453A – Tablet OOS for weight on the QA Over Check Data Sheet[23]
   - 80224A1 and 80227A1 – " is having an OOS issue with high weights, and these batches are suspect."[24] Note: these batches were finished and packaged and now QA was questioning the acceptability of the lots
   - 80228A1 – Investigation # 08-060 :"17 tablets with higher weight out of 30 tablets"[25], discovered in Packaging

2. Other Quality Problems with Digitek lots:
   - 70926A1 and 70953A1 "have Assays too low"[26]
   - 80044A1 – a stainless steel screw was found in tablet well during packaging (the compression process, which includes metal detection, did not detect the presence of a huge metal particle)
   - 80051A – Spots on tablets[27]
   - 80053A – Did not record metal detector and there is no record that the lot was reprocess through the metal detector
   - 70148A, and 70207A Digoxin Tablet 0.125 mg OOS[28] for blend uniformity
   - 70078A1 – Time zero (i.e. very beginning test) stability test results not recorded[29]
   - 70770A - OOS results for high RSD

[21] Exhibit #M-16 - Certificate of Conformance, Dan Bitler QA Director, dated 3/31/08
[22] Plaintiff's #143 – Re: Digitek batches on HOLD, Suzanna Wolfe, 4/2/2008
[23] Exhibit Plaintiff's #133 – Scott Talbot, Email Subject: Status Report – September 27, 2007, 9/27/2007
[24] Exhibit #143– Suzanna Wolfe, Email Subject: Digitek Batches On Hold, 4/2/2008
[25] Exhibit Plaintiff's 141 – Investigation # 08-060, No Author, No Date
[26] Exhibit # M-14 – Suzanna Wolfe, Email Subject: Digitek parameter review, 1/4/2008
[27] ACTAV 001868986 – 2008 Riverview Investigations, No author, No Date
[28] ACTAV 001869221 - Annual Product Review for 0.125 Digoxin Tablets, 3/17/08
[29] ACTAV 001580762 – Open Investigation Report – No Author, No Date, 4/30/2008 or more recent

- 70207A – Blend failure that was "Released"[30]
- 80108A –QA inspector verified wrong incorrect bar code[31]
- 800152A and 080154A – Process Validation protocol issues
- 70736A - OOS[32] for STR for Content Uniformity
- 70080A, 7081A, 70082A – High Impurity Level[33] – These batches were released. "All of them showed the high impurity result for Digoxigenin. It should have been a STR investigation and nobody did nothing (anything)"
- 80133A – Operator noticed that tablets were thinner during a routine inspection of a finished drum

These total 24 lots (seven (7) of which were OOS for thickness and/or overweight) of Digoxin with Quality problems, including OOS. Some of the lots were released, including OOS lots. This is an extraordinarily high incidence of significant problems, most of which are within a two (2) year period. This is especially concerning because Analyst records show that Digoxin is one of the "top 3 products in term of number of Adverse Event Reports where product was associated with a death or permanent injury outcome Digoxin 0.25mg[34]

3. 2007 Lab OOS - There were over 100 reported OOS within the QC Laboratory for 2007. A total of three (3) were specifically for Digoxin. *QC Laboratory 2007 OOS (Log) (Document 3006414)*[35]
4. 2008 Lab OOS - There were over 100 reported OOS within the QC Laboratory for 2008. A total two (2) were specifically for Digoxin. There was no apparent improvement when compared to the prior year. *QC Laboratory 2008 OOS (Log) (Document 3006420)*[36]
5. 2007 Investigations - There were over 100 Nonconformances that required a formal documented investigation. *Investigation Log 2007*[37]
6. 2008 Investigations - There were over 224 reported Nonconformance that required a formal documented investigation in *Investigation Log 2008*[38]. A total of ten (10) were specifically for Digoxin. There was well over a 100% increase compared to the prior year. Based upon this significant increase, GMP Compliance appeared to be progressively deteriorating.
7. 2008 Open Investigations(7 month period)[39] - There were 94 open product investigations for serious issues, the vast majority for product OOS
8. 2008 – 2009 (12 month period) Deviations - There is a 59 pages summary report that lists the unplanned *Deviations List Report* [40]that were conducted from 12/5/08 – 11/10/09 (12 month

[30] Exhibit 183 – Wanda Eng. Email Subject: Blend Failure locations, 7/20/2007
[31] ACTAV 001868986 – 2008 Riverview Investigations, No author, No Date
[32] ACTAV 001869221 - Annual Product Review for 0.125 Digoxin Tablets, 3/17/08
[33] Exhibit 172 – Email Subject :RE: Please explain, Jisheng Zhu, 3/19/2008
[34] Exhibit Plaintiff's #249 – Sarita Thapar, Email Subject: FW. Insurance Questions, 10/1/2007
[35] Document 3006414 – QC Laboratory 2007 OOS (Log)
[36] Document 3006420 – QC Laboratory 2008 OOS (Log)
[37] Document 3005608 – Investigation Log 2007
[38] Document 3005503 – Investigation Log 2008
[39] Document ACTAV 001580756 – Open Investigations (9/2007 – 3/2008)

period). There were a total of 247 unplanned deviations. At Actavis unplanned deviations are initiated when a batch/material/procedure is nonconforming/OOS and management determines if they wish to accept the nonconformance/OOS and continue to process the product, ultimately for release to the market place

9. 2006 – 2007 Rejections (17 month period) – According to *Rejected Batches from August 2006 through 2007 (17 months)*[41] there were approximately 20 batches rejected. This number is alarming, but not unexpected due to the high number of OOS, Deviations, and nonconformances over the same period of time. The greater issue is not the number of rejected batches (since these were caught) but the potential that other batches (that should have been rejected) were released for sale.
10. 2007 – 2008 OOS (8 month period) - There were a total of 96 OOS results that were recorded during the period of 9/07 – 4/08, according to an investigation report issued April 15, 2008[42]. This is an extraordinary number of OOS. During this eight (8) month period a total of nine (9) OOS involving 14 Digoxin lots. The OOS results were in multiple manufacturing and control areas.
11. Blending OOS - There were a total of 19 lots with product blending OOS[43]. As a result of the investigation, 6 lots were rejected, 6 were released for sale and 8 were still on hold (as of 7/20/2007). This number of blending nonconformances should have triggered a systematic review of the blending processes and then questions whether or not the processes are adequately validated. It should be noted that two (2) of the lots are Digoxin. One was released for sale. By contrast, most pharmaceutical operations have few if any blending OOS; however, if they occur, a comprehensive investigation and CAPA is implemented. These batches are usually destroyed because the OOS invalidates the process validation work done previously.
12. Investigation Review Board – Open Deviation Report [44] – On March 23, 2008 there were 53 open investigations into OOS. A total of 28 investigations into OOS were open for more than 50 days. Many were open for more than 100 days. The number of investigations is concerning; however; their length open is more concerning. Investigations of OOS must be completed quickly for several reasons. The longer the wait, the less probability that the root cause can be determined. Even more important is that this lengthy investigation has the potential to impact a much greater scope (than the specific batch of raw material or product). For example, if the OOS investigation determines that a commonly used instrument or test method does not provide accurate results, then the effects of this problem must be determined. If an investigation is done at day 100, then all of the tests conducted using this instrument and test method are suspect. The investigation into this type of event would be difficult with potentially widespread implications. Another example is process water used in product. If there was an OOS with water quality and the investigation was not conducted until 100 days later it must be determined the effect the OOS has on all product made since the OOS. Water is used in most

[40] Document 3005547 – Deviation List Report (Log)
[41] Document 5475428 – Rejected Batches from August 2006 through 2007
[42] Exhibit Plaintiff's #217 – Mishbah Sherwani, Email Subject: FW: List by Product, 4/15/2008
[43] Exhibit 183 – Wanda Eng, Email Subject: Blend Failure locations, 7/20/2007
[44] Exhibit Plaintiff's #216 – Michael Ponzo, Email Subject: FW: Investigation Review Board Meeting *Rescheduled* UPDATE*, 3/28/2008

drug products. How do you investigate all of the products manufactured since the start of the OOS?

13. Ineffective Stability Testing Program

In the FDA documentation and correspondence, there were numerous products that failed the Stability Testing. Additionally, there were numerous mistakes associated with the testing.

It is important to understand that Stability Testing and subsequent analysis of the data, is the primary method to determine the shelf life (i.e. expiration date). Ongoing Stability Testing of marketed products is the primary method to verify that the product's labeled shelf life is correct. When a product tests OOS then the entire product in the market is suspect until an investigation is complete. After the investigation, it will be determined what the range of the issue is. When there is a breakdown of the Stability Testing Program, the quality of the product in the marketplace might not be assured.

14. Process Validation

"Approximately 25% of the commercial manufacturing equipment has not been qualified."[45] Process validation provides evidence that each product (bulk, tablets and packaging) conform to requirements and that sampling (such as in Stability Testing) is a valid method to determine the quality of all digoxin products. Since it was determined that many of the processes were not adequately validated, this further exacerbates the overall concerns and establishment of shelf life.

15. Product Recalls

The nonconforming product was of sufficient risk to the public to warrant the recall of all Digoxin products in the market. The reason for the recall is summed up in the following: "She stated that the reason the recall was expanded to all Digitek was that FDA felt that there weren't adequate controls on their tablet presses to assure that the double-thick tablet issue couldn't have happened previously"[46]

16. Mitigating Actions

In reading hundreds of Actavis documents, there is no mention to the implementation of immediate actions to mitigate the current risk. Within the drug industry, this is a highly common action when nonconformance occurs; especially, when the nonconformance is identified at a later stage of processing. For example, if a double thick tablet is found at packaging, it would be reasonable to assume that it was not picked up by the controls that were in place at compression (tablet making). There should have been consideration to having temporary inspections conducted at greater frequency by the operator and QA inspector (at compression and packaging). Although this type of mitigating action will not eliminate the source of the nonconformance, it will increase the probability of detecting the defect. This type

[45] MLYN 000032279 - FDA 483 for Little Falls NJ - Issued by the Parsippany NJ office, 12/1/04

[46] Exhibit #M-5, Email Subject: Actavis (Amide) Recall and FDA Inspection, Chuck Koon (Vice President of Quality Assurance at Mylan), 4/27/2008

of action is short term but may help reduce the risk but it will not eliminate defects. Likewise, there was no mention to investigating automatic weighing to potentially detect each defect. Early detection will greatly increase the probability of finding the root cause of the nonconformance.

Quality & Quality Systems
SpyGlass Group Summary

It is my opinion to a reasonable degree of certainty that Actavis failed to establish reliable and GMP compliant systems and procedures resulting in the release of adulterated product from at least the period of 2004 – 2008.

c. Double Thick Complaint Lot 3611A

Double Thick Digoxin Tablets 0.25 mg – Lot 3611A

2007 Investigation No: 04-003 – Complaint Investigation

FINDINGS

Investigation Report 04-003[47] summarizes the results from a customer complaint received by Actavis on 7/7/04. A pharmacist returned a 0.25 mg Digoxin tablet from Batch # 3611A which was approximately twice normal thickness and weighed twice as much. Two Stokes compression machines were used on Batch # 3611A. Under normal operation these machines cannot make double thickness tablets. Upon machine set up however, double thickness tablets can be made. In this case double thickness tablets are observed by the set up operator who adjusts the machine and thinks he/she cleared the area of any double thickness tablets prior to actual production startup. QA's inspection did not detect the defect. The compression operation begins and lasts for several days until the bulk blended batch is exhausted. There are several long interruptions in the tableting process; the most significant is a stop for cleaning where the punches are removed and the equipment is then readjusted. QA then occasionally monitors the quality of the product and conformance to procedures. The batch size target is about 4.8 million tablets and a single batch of digoxin tablets can take several days to compress.

Investigation 04-003 concluded the most probable cause of double thick tablets was that they were made during the initial setup, the single tablet returned became stuck in the deduster and was not removed or detected prior to starting the production run.

The following identifies some of the serious issues with the actions and documentation associated with Complaint Investigation Report 04-003

- Approval by Top Management: - The Investigation Report is not signed and dated. The Investigation Final Report was never approved by Senior Management as required by the SOP. The SOP requires the following management approvals:
  - Quality Assurance Director
  - Vice President Scientific Affairs
  - Manufacturing Operations Director

  This is a violation of cGMP. An undated and unapproved/unsigned document does not provide formal/legitimate evidence that the right things were done.
- Corrective Action Dates – There are no dates associated with the corrective action
- Analysis of the Complaint Sample: There was no analytical testing of the complaint sample

[47] Exhibit Plaintiff's #128 – Amide Pharmaceutical, Inc. Investigation Final Report No. 04-003, Initiated 7/9/04

- Critical Corrective Action - The investigation documents do not list the procedures, etc. that were corrected. The document should not have been approved unless there was specific reference to the document(s) that were corrected. There should also have been a documented verification on the effectiveness of these changes.
- Undisciplined & Inadequate Investigation – The investigation does not follow any generally accepted problem solving approach or method. The root cause was never identified, yet the investigation only focused on cleaning the deduster and chutes at start-up. There are many more potential root causes that were not considered.
- Inadequate Investigation and Corrective Action – The corrective action was not effective as was evidenced by a repeat double thick tablet incident (Lot 709241A1/A2)

DOUBLE THICK COMPLAINT LOT 3611A
SPYGLASS GROUP SUMMARY

It is my opinion based upon a reasonable degree of certainty that Actavis demonstrated general inability to handle this critical product quality crisis. Had the proper investigation been performed, a root cause would have been determined and the weak links in their practices might have permanently resolved the double thickness matter. In 2004 Actavis released product with serious defects. Actavis' response to this serious issue was not adequate and the actions did not comply with the GMP Regulations. The complaint samples might have been double or more of the labeled dosage. Based upon the lack of GMP controls in place at the plant, there is no reason to believe that this was an isolated incident. There was inadequate investigation; therefore, the problem was likely to resurface. The same problem did resurface in 2007.

d. Lot 70924 2nd Report of Double Thickness Tablets

Report of Double Thickness Digoxin Tablets 0.125 mg - (Lot #70924A1/A2)

2007 Investigation Log # 70-093[48]

FINDINGS

The chronology of the events associated with the double thick Digitek tablets is as follows:

The double thickness Digitek problem surfaced again on 11/30/2007 when five (5) double thick tablets were discovered while in the middle of packaging the lot. It is important to note that the double thick tablets were never detected at tableting. Packaging continued with the QA instructions "If one or two thick tablets found, continue packaging operation with a watchful eye."[49] This clearly was inadequate direction. During the packaging a total of 15 additional double thick tablets were found in drums 15/16, 17 and 34. On 12/04/2007 this packaged batch was released for sale. On 12/05/2007 this batch was placed on hold by QA. On 1/11/2008 the batch was salvaged by 100% visual inspection. On 1/22/2008 the lot was sampled by QA, no additional tablets were found. On 1/23/2008 the inspected batch was approved for packaging. On 1/28/2008 the batch was approved by QA. See the *Appendix C – Chronology of Lot 70924 – Double Thick Lot.*

FDA issued a 483[50] on an inspection of 993 Riverview Drive from an inspection from 3/18/08 to 5/20/08 with 11 major observations. Observation 2 states that "Drugs products fail to meet established specifications and quality control criteria are not rejected." Specifically it states in 2a. "During packaging of Digoxin Tablets 0.125 mg, lot #70924A1, five double thick tablets were observed. Quality Assurance approved a 100% visual inspection of the 4.8 million tablet lot which resulted in an additional 15 double thick tablets. Although Quality Assurance was aware of the "double thick' tablet findings, the batch was then released based on AQL sampling which included visual inspection of 1330 tablets. No root cause was determined for the defect; however the lot was released to the market by the Quality Unit on 1/28/08 following the visual inspection. There was no documented evaluation of the approximately 89 lots remaining on the market at the time of inspection." The FDA had grave concerns about all 89 lots that were released for sale to the public. The facts of this situation ended with a mandate for full product recall.

There are many issues associated with the handling of the double thickness issue.

[48] Plaintiff's Exhibit #16 – Investigation Report #07-093, Batch #70924, 12/5/2007
[49] Incident Report; from Packaging Manager and Supervisor, 12/1/2007
[50] Plaintiff's Exhibit #91 – FDA EIR, inspection of 8/18 to 5/20/2008

Unexplained Decisions

- When the defective tablets were later discovered in packaging, the packaging operation was allowed to continue. The operation should have been immediately halted. All products made to that point should have been immediately placed on hold and properly labeled as such. There should have been no further processing until a comprehensive investigation was conducted.
- On 12/4/2007 uninspected finished product lot containing defects was released for sale by Quality Assurance. A day later (12/05/2007), QA reversed their decision and decided that the batch was not acceptable and should not be distributed. How could an event like this occur in a well controlled environment? This is a breakdown of the highest order. The distribution of the lot was halted and the product lot was placed back on hold without any documented reason for this action. This incident alone should have been classified as a serious high priority nonconformance and properly investigated, including a potential CAPA. The batch was subsequently salvaged by breaking down the package, saving the tablets, visually inspecting the lot to eliminate defects, repackaging and then re-releasing the salvaged batch. The justification for these actions was not documented.

Inadequate Quality Problem Investigation

- Root cause of the problem was never confirmed but "appeared" to be caused at compression machine startup.
- Tablet compression was on 2 Stokes Presses over a 3 day period. The presses were stopped a total of 18 times for breaks, lunch, and overnight with very few QA checks on restart. Stoppages ranged from 20 minutes to 17 hours.
- Actavis identified the lack of cleaning of the deduster at compression startup as a potential root cause; however, records indicate that this may not be correct. A total of 20 double thick tablets were found in the batch. Their Investigation 07-093[51] determined that the only opportunity for this to occur was at compression startup. This conclusion may be flawed. Five (5) tablets were found in the first inspection process in buckets #15 &#16 (2 tablets within both buckets), #17(1 tablet), and #34(2 tablets) and in 100% inspection another 15 with no locations noted. This indicates that the problem occurred throughout tableting or original filling process and not just at startup. This information was never even considered during the root cause analysis. Again, how could these all be the result of startup when they were spread throughout many buckets?
- Investigation is incomplete and never included other potential root causes to the production of double thick tablets, including:
    - There is no documented investigation into complaint history for similarly manufactured tablets, including other tablet product made by the same or similar process and equipment
    - Double thick tablets were never chemically tested. The dose of the double tablets is not known.
    - No review of records to determine if the equipment is qualified and the process validated
    - No review of the training records of the associates

[51] ACTAV 000002766 – Memo Subject Investigation 07-093, Michael Manzo, 1/8/08

- No consideration of design changes to the equipment to eliminate future defects
- No review of the proper use of defect buckets and labeling practices
- No detailed review of the history of this type of nonconformance
- No clear conclusions resulting from the investigation
- No investigation into the history of changes to the equipment
- No review of the preventive maintenance of the tableting equipment
- No inspection of the other lots of Digoxin tablets within their control or on the market

- There was no subsequent increase in QC checks or other controls (intended to add further probability to detect double thickness tablets). Some steps should have been implemented to mitigate the risk since the root cause of the problem was never determined.
- Unexplained Increase in Quantity after Packaging - The records show that the repackaged batch had an increase in the quantity after 100% inspection and repackaging. An unsigned and undated memo[52] from Ashesh Dave attempts to explain the discrepancy. The investigation was not extensive merely focusing on weigh errors.

Ineffective and Unreliable Methods to Salvage a Known Defective Tablet Batch

- Production and Quality Assurance used a method to salvage a defective batch (containing double thick tablets) that is generally not accepted in the drug industry as being effective, i.e. their method for attempting to cull out 100% of the defects within a 4,800,000 tablet batch through human 100% visual inspection. This method of visually inspecting out defects is known throughout the medical products' industry to be unreliable. It is one of the more famous quotes that 100% inspection is no better than 80% effective. Said another way, 100% Inspection is not 100% effective. Based upon this industry's accepted understanding, it is almost certain that further defective tablets remained in the batch. (Ref. Juran[53] and Craig QP 2004 July[54])

- After 100% inspection, the batch was subjected to another QA inspection using a tightened AQL where each of the 34 individual buckets from the batch was randomly sampled[55] with 40 tablets each. After visual inspection, a Quality Control sample inspection was designed to allow less than 100% effectiveness. The batch could be released even if a defect was found in the final QA samples (i.e. the lot would pass if one (1) defective tablet was found in the samples, only rejecting if two (2) or more defective tablets were found.) The "tightened "AQL testing plan would have released the batch even if one defective tablet was found. What was QA and Management thinking?

- There is no documented procedure that describes the equipment, techniques and methods used in the 100% visual inspection.
- There was no Quality Assurance monitoring of the visual inspection.

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[52] Disposition Exhibit -#168 – Subject: An explanation for two additional bottles in the final yield after repackaging of the batch, Not Date

[53]Quality Control Handbook, J.M.Juran, 3rd Ed. , 1951, McGraw-Hill, pp. 12-61 to 12-63. On 100% Inspection Accuracy

[54] , Quality Progress, D.J.Craig, July 2004. On 100 % Inspection Accuracy.

[55] Sampling Plan - The sample and test plan was as follows: AQL level = 0.065, Sample Plan= single, tightened level 1, Sample Size Code = Q, Bulk Size ~ 4.8 million, Inspect 1250 tablets minimum from 34 drums. 40 from each of 33 drums, 10 from 34th drum. Tablets taken at random, Accept on 1/reject on 2 of total batch

- There is no documentation that the inspectors were properly trained on the inspection method
- The salvage method was not properly approved. There was no approved Deviation Record to authorize the procedure of tearing down finished product and 100% inspecting.
- There is no record that the visual inspection procedure is effective. The procedure was never qualified. How thick does a tablet have to be identified in a 4.8 million tablet lot?
- The acceptance criteria for 100% inspection not established. How thick was too thick?

Inadequate Batch Record Detail of the Lot Salvaged Through 100% Inspection

- There is no documented evidence that the defective lot was properly salvaged. For example, the following required information was not included in the batch record:
  - Inspection Start and End Date/Time
  - Name and document number of the 100% inspection procedure/method
  - Startup inspection
  - Clean up inspection
  - In-process Quality inspection monitoring
  - Inspector's names
  - Inspector's training records
  - Deviation authorization number
- The inspection protocol did not include the required information, for example:
  - Inspection Procedure
    - What is the Quality Standard
    - Were the tablets spread out on a tray?
    - Did they have increased light or other enhancements for visual improvement?
    - Did they need to wear gloves?
    - How did they transfer the tablets?
    - How did they segregate the double thick tablets?
    - What if other defects are discovered (black spots, broken, discolored)? Are these noted in the records? How will it be handled?
  - Acceptance Criteria and Specifications
  - Responsibilities
- The activities were handled according to incomplete and disjointed memos and apparent verbal instructions.

LOT 70924 2ND REPORT OF DOUBLE THICKNESS TABLETS

SPYGLASS GROUP SUMMARY

- Batch # 70924 should have been rejected and destroyed. There is no confidence that the process was capable of producing defect free tablets. The methods and procedures in place during the production of Lot 709241A were not in compliance to FDA GMP Regulations. It is not possible to defend management's action in this regard.
- Significant violations of GMP contributed to the production of a lot containing critical defects, i.e. "double thick tablets".
- After the discovery of tablet defects, the lot was not destroyed. In fact, there appeared to be continuous waffling back and forth in terms of the correct disposition of the batch.
- In the attempt to salvage 4,700,000 tablets, the defective batch was further processed using ineffective and unvalidated methods that would not have provided a high level of assurance that the lot was defect-free. Among the unvalidated methods, a human 100% inspection process is not effective and will not remove all defective tablets, especially in such a large batch. Can you visualize operators looking at millions of tablets? It was in some ways like trying to find a needle in a haystack.
- Because the investigation was inadequate, the corrective action may not be effective in preventing recurrence of the double thick tablets.
- I challenge the wisdom in the decision to release Digitek, digoxin 0.125 mg, Batch # 70924 for sale. I challenge the decision not to reject and destroy the batch. As with many other nonconformance, deviations and OOS, a root cause determination was not evident and the corrective action to prevent recurrence was either not effective or never implemented. An experienced Quality Assurance Head would not have followed the Actavis decision making path.

e. FDA Observations & Other Events

The Federal Government cited Actavis for serious GMP violations in at least 6 FDA inspections over a period of 2004 to 2008 issuing a Permanent Injunction on 11/12/08. This injunction shut down the plant.

FDA records demonstrate that there were unacceptable and noncompliant practices for a six (6) year period. An analysis of the FDA 483's, Warning Letters and Permanent Injunction confirm that there were repeated nonconformances in the fundamental control systems; including,

- Quality System
- Facilities & Equipment System
- Production System
- Laboratory System
- Regulatory Requirements

The observations are summarized in *Appendix F – FDA Observations & Events.* A review of this document will confirm the pattern of repeat nonconformance.

The following summarizes some of the system issues identified by the FDA.

Quality System

The FDA identified Quality System issues in every 483 report. The observations included:

- Changes made to records without approvals
- Inadequate investigations of complaints
- Inadequate investigation of nonconformances
- Failure to prevent the release of lots with significant nonconformances
- Batch failures not investigated

Facilities & Equipment System

- 25% of the manufacturing equipment is not qualified
- Inadequate preventive maintenance program
- Equipment qualification issues

Production System

- Lack of Cleaning Validation
- Production documentation not controlled to protect unauthorized changes
- Inadequate inprocess testing
- Deviations from production and process control

- Records not complete
- Inadequate storage practices
- Procedures not followed

Laboratory System

- Stability Testing Protocol not followed
- Unsecure computer records
- Quality testing records incomplete
- Changes to lab notebooks after it was approved
- Original OOS results not recorded
- Lab computer system is not validated
- Examples where products did not meet specification throughout the product's shelf life
- Lab controls that are not scientifically sound

Regulatory Requirements

- Adverse Drug Experience (ADE) information not reported to the FDA
- ADE not investigated
- Procedures not established for post marketing ADE
- Field Alert Reports not submitted on time

SPYGLASS GROUP SUMMARY

Over the 2004 – 2008 time periods, all products made at Actavis were in violation of GMP and are therefore adulterated.

The root cause of complaint and product issue is invariably linked to GMP nonconformance. The lack of an effective Quality System creates and unacceptable Product Quality & Regulatory Compliance risk.

This repeat pattern of serious violations to GMP, the release of nonconforming product and the FDA's intolerance to the continuation of this unacceptable public risk, resulted in a court ordered closure of the plant.

There was a general lack of well-established Quality Systems. The importance of a well established Quality Systems cannot be overstated. My experience is that the lack of a Quality System creates an environment where defective products can be produced and subsequently released to the market.

f. Recall.

A review of Appendix *F – Summary of FDA Observations and Events* will confirm that serious violations occurred, including the release of Digoxin that failed to meet established standards and specification and other relevant quality control criteria. As a result of the FDA concerns, a complete recall of all Digitek lots was conducted. See *Appendix D Press Release – Digitek Product Recall 25-APR-2008.*

A review of Appendix *F – Summary of FDA Observations and Events* will confirm that serious violations occurred, including the release of many products that failed to meet established standards and specification and other relevant quality control criteria. As a result of the FDA concerns, a recall of 66 different products was conducted. See Appendix *E – Press Release – Products Manufactured at Little Falls)*

g. Mylan

Responsibilities (Quality Agreement)[56] – Mylan never established a written agreement between both companies that stated each other's responsibilities and the action steps for complying with the GMP regulations. On about 1/29/2007 Mylan attempted to establish responsibilities between each company which is years after starting their business together. It is difficult to understand that it took eight (8) years to realize that their mutual responsibilities and accountabilities had not been established.

Complaint Handling – Mylan is the company responsible for fielding customer complaints, including medical complaints. Mylan is then required by GMP to investigate all complaints. In the case of Digoxin, it would be expected that Mylan share the complaint information and then require Actavis to perform their investigation. This should be done in accordance to a mutually approved Quality Agreement. Actavis would then communicate their findings and if applicable corrective actions. There is no evidence to demonstrate that Mylan detected the lack of an adequate investigation and corrective action to the double thick complaint.

GMP Auditing of Digitek - The records demonstrate that one GMP audit[57] of Actavis was conducted by Mylan. This audit focused on Digoxin. Most drug companies audit their external manufacturers at a frequency of once every 1 – 2 year period unless there is documented justification to decrease the frequency. It does not appear that Mylan met this industry norm. There is no evidence that the audit was a systematic review of the required GMP control systems as is the norm in the industry. There is no evidence that the audit included a review of deviations, nonconformances, specifications, lab testing records and batch history records as is the norm in the industry. On the contrary, the audit appears to be a plant tour and an onsite update of Actavis' FDA related activities. There is no GMP audit agenda nor is there any indication that any section of the GMPs was audited.

It is my opinion to a reasonable degree of certainty and based upon reviewing the records of over two hundred drug and device companies (including dozens of contract manufacturers) that Mylan did not have in place the minimum control systems for qualifying and monitoring contract manufactures as required by

[56] Exhibit #M-23 – Document from Mylan, No name identified (Potentially P. Latzo), about 1/29/2007
[57] Exhibit # MYLN 000030 (number not clear) – R. Pinnell and P. Streater, Audit Number: XA-06-010, 12/04/06

GMP. Additionally, one audit within a 9+ year period is not adequate to ensure that companies producing Mylan's products fully meet GMP requirements.

It is my opinion to a reasonable degree of certainty, that if Mylan had conducted GMP audits (using a highly qualified GMP auditor or audit team) prior to awarding the contract and 1-2 years thereafter, then they would have detected the GMP issues prior to the FDA's series of inspections and subsequent escalation activities.

Expert Witness Final Summary

There were critical quality and Good Manufacturing issues identified at almost every point in the production, control and testing processes. There was a breakdown in their Quality Systems that allowed mistakes and errors in judgment to occur. Over at least a four (4) year period, Actavis released adulterated product, including Digoxin.

It is my opinion to a reasonable degree of certainty that the GMP Compliance and Quality problems might have been averted if early in the problem discovery phase, management had taken appropriate actions, including placing priority on the fixes. Based upon the records, they were constantly fighting ever increasing fires and continually being faced with nonconforming product and noncompliant practices. Faced with the responsibility of making high Quality products while trying to put out the fires eventually became an insurmountable task.

It is my experience that good people don't come to work with the intention of doing a bad job. It is the company's misguided values, principles and work-ethics (established by Actavis top management) that fostered bad behavior. The Actavis environment was not focused on GMP and Product Quality; therefore, all involved suffered the adverse consequences.

As quoted earlier "This is all rather sad. Looks like some very basic GMP knowledge was lacking."

Mark G. Kenny

Managing Director

SpyGlass Group, Inc.

6/15/2010

Date

Appendices

A. Mark G. Kenny CV
B. References
C. Chronology of lot 70924 – Double Thick Lot
D. Press Release – Digitek Product Recall 25-APR-08 (Recalled)
E. Press Release – Products Manufactured at Little Falls (Recalled)
F. Summary of FDA Observations and Events

Appendix B - References

1. Quality & Compliance Consulting Group – website: www.spyglassgroupinc.com
2. 21 CFR Part 210 and 21 CFR Part 211 Current Good Manufacturing Practice for Manufacturing, Processing, Packing, or Holding of Drugs and Finished Pharmaceuticals
3. FDA Form 483, Issued to Divya C. Patel (President), District FDA Office in Parsippany - NJ, 12/1/042004
4. Plaintiff's Exhibit #82, Complaint of Permanent Injunction, 11/14/08
5. Plaintiff's Exhibit #124 – Definition of an adulterated drug, US doc. 351.
6. Appendix D Summary of FDA Observations & Events
7. http://www.cgmp.com/warningLetter.htm
8. http://www.actavis.com/en/products/manufacturing/good+manufacturing+practice.htm
9. Plaintiff's Exhibit #147 – Email Subject: Form FDA 483 RV.pdf, Jacob Haroon, 5/27/ 2008
10. Complaint for Permanent Injunction, Case 2:08-cv-05656-SDW-MCA, Christopher Christie (United States Attorney), Filed 11/14/2008, p 11
11. Exhibit Plaintiff's #146- Email Subject: Totowa Potential 483 items and comments, Wanda Eng, 4/17/2008
12. Plaintiff's Exhibit 229 – Warning Letter, Douglass Ellsworth, August 15, 2006
13. Mylan Audit, Subject: Final Corrective Action Memo, from R. Pinnell, 1/23/2008
14. Exhibit Plaintiff's #137 – Totowa Action Plan (August 2006 GMP Inspection Totowa), Not dated - estimated July 2007
15. Plaintiff Exhibit #25 – Revised Warning Letter, 2/2007
16. Exhibit Plaintiff's #106 - Subject: FDA Little Falls Inspection Closeout – May 20, 2008, Garret R. Woolan – Scribe, 5/20/2008
17. ACTAV 000484606 – Quality System Improvement Plan, 2/26/2009
18. Plaintiff's #175: M. Patel, Email Subject: Regarding internal cGMP audit, 1/25/2008
19. Plaintiff Exhibit #25 – Revised Warning Letter, 2/2007
20. Exhibit Plaintiff's #92 – Presentation at a Feb 2006 Sales Meeting, Not Dated
21. Exhibit #M-16 - Certificate of Conformance, Dan Bitler QA Director, dated 3/31/08
22. Plaintiff's #143 – Re: Digitek batches on HOLD, Suzanna Wolfe, 4/2/2008
23. Exhibit Plaintiff's #133 – Scott Talbot, Email Subject: Status Report – September 27, 2007, 9/27/2007
24. Exhibit #143– Suzanna Wolfe, Email Subject: Digitek Batches On Hold, 4/2/2008
25. Exhibit Plaintiff's 141 – Investigation # 08-060, No Author, No Date
26. Exhibit # M-14 – Suzanna Wolfe, Email Subject: Digitek parameter review, 1/4/2008
27. ACTAV 001868986 – 2008 Riverview Investigations, No author, No Date
28. ACTAV 001869221 - Annual Product Review for 0.125 Digoxin Tablets, 3/17/08
29. ACTAV 001580762 – Open Investigation Report – No Author, No Date, 4/30/2008 or more recent
30. Exhibit 183 – Wanda Eng. Email Subject: Blend Failure locations, 7/20/2007
31. ACTAV 001868986 – 2008 Riverview Investigations, No author, No Date

32. ACTAV 001869221 - Annual Product Review for 0.125 Digoxin Tablets, 3/17/08
33. Exhibit 172 – Email Subject :RE: Please explain, Jisheng Zhu, 3/19/2008
34. Exhibit Plaintiff's #249 – Sarita Thapar, Email Subject: FW. Insurance Questions, 10/1/2007
35. Document 3006414 – QC Laboratory 2007 OOS (Log)
36. Document 3006420 – QC Laboratory 2008 OOS (Log)
37. Document 3005608 – Investigation Log 2007
38. Document 3005503 – Investigation Log 2008
39. Document ACTAV 001580756 – Open Investigations (9/2007 – 3/2008)
40. Document 3005547 – Deviation List Report (Log)
41. Document 5475428 – Rejected Batches from August 2006 through 2007
42. Exhibit Plaintiff's #217 – Mishbah Sherwani, Email Subject: FW: List by Product, 4/15/2008
43. Exhibit 183 – Wanda Eng, Email Subject: Blend Failure locations, 7/20/2007
44. Exhibit Plaintiff's #216 – Michael Ponzo, Email Subject: FW: Investigation Review Board Meeting *Rescheduled* UPDATE*, 3/28/2008
45. MLYN 000032279 - FDA 483 for Little Falls NJ - Issued by the Parsippany NJ office, 12/1/04
46. Exhibit #M-5, Email Subject: Actavis (Amide) Recall and FDA Inspection, Chuck Koon (Vice President of Quality Assurance at Mylan), 4/27/2008
47. Exhibit Plaintiff's #128 – Amide Pharmaceutical, Inc. Investigation Final Report No. 04-003, Initiated 7/9/04
48. Plaintiff's Exhibit #16 – Investigation Report #07-093, Batch #70924, 12/5/2007
49. Incident Report; from Packaging Manager and Supervisor, 12/1/2007
50. Plaintiff's Exhibit #91 – FDA EIR, inspection of 8/18 to 5/20/2008
51. ACTAV 000002766 – Memo Subject Investigation 07-093, Michael Manzo, 1/8/08
52. Disposition Exhibit -#168 – Subject: An explanation for two additional bottles in the final yield after repackaging of the batch, Not Date
53. Quality Control Handbook, J. M. Juran, 3rd Ed., 1951, McGraw-Hill, pp. 12-61 to 12-63. On 100% Inspection Accuracy
54. Quality Progress, D. J. Craig, July 2004. On 100 % Inspection Accuracy.
55. Sampling Plan - The sample and test plan was as follows: AQL level = 0.065, Sample Plan= single, tightened level 1, Sample Size Code = Q, Bulk Size ~ 4.8 million, Inspect 1250 tablets minimum from 34 drums. 40 from each of 33 drums, 10 from 34th drum. Tablets taken at random, Accept on 1/reject on 2 of total batch
56. Exhibit #M-23 – Document from Mylan, No name identified (Potentially P. Latzo), about 1/29/2007
57. Exhibit # MYLN 000030 (number not clear) – R. Pinnell and P. Streater, Audit Number: XA-06-010, 12/04/06
58. Deposition of Chuck Koon – Dated 5/21/2010, No exhibit number
59. http://www.actavis.us/en/media+center/newsroom/articles/digitek+recall.htm
60. http://www.actavis.us/en/media+center/newsroom/articles/Actavis+Totowa+Recall.htm

Appendix C – Chronology of Lot 70924 – Double Thick Lot

Date	Action
11/12/2007	Digitek Lot Number 70924A was started – Theoretical batch size of 4,800,000
11/16/2007	Tablet Compression Machine was set up
11/17/2007	Started Compression (one operator was running 2 tableting lines)
11/18/2007	Finished Containers 1 – 14
11/19/2007	Stopped, removed and cleaned upper and lower punches due to excessive build-up of powder (press 67)
11/19/2007	Finished Containers 15 – 26
11/20/2007	Finished Containers 27 – 34 (final container)
11/29/2007	Packaged 4,754,000 million tablets
11/30/2007	Two tablets found on line #405. Two prior buckets inspected with no additional double thick. Packaging resumes. QA instructed "If one or two thick tablets found, continue packaging operation with a watchful eye". A total of 5 double thick tablets were found. (buckets 15/16, 17 and 34)
12/01/2007	Competed, found "only" one tablet from Bucket # 17
12/01/2007	Finished stock transfer sheet completed to move product into accepted status
12/04/2007	Finished product approved and formally released by QA
12/05/2007	Batch placed on hold
1/11/2008	Bitler issues Inspection Protocol authorizing 4,722,000 tablets to be inspected
1/18/2008	Repackaged batch passed the reinspection requirements (a total of 15 double thick tablets were found during 100% inspection)
1/21/2008	QA Sample Inspection protocol issued
1/22/2008	QA Sample Inspection completed – no double thick tablets found in sample
1/23/2008	Ashesh Dave issues email stating that the line operator found thick tablets previously at packaging and is requesting to repackage the lot
1/23/2008	Finished product acceptable
1/24/2008	Packaged 4,754,000 salvaged tablets
1/24/2008	Ponzo issues an investigation summary
1/25/2008	Batch accepted/authorized for repackaging (Dan Bitler approved) AFTER repackaging
1/28/2008	Lab results indicate acceptable
1/28/2008	Batch released
1/30/2008	Batch shipped

Appendix D – Press Release – Digitek Product Recall 25 APR 2008

Actavis Press Release[58]

Actavis Totowa (formerly known as Amide Pharmaceutical, Inc.) recalls all lots of Bertek and UDL Laboratories Digitek (digoxin tablets, USP) as a precaution

Morristown, NJ, 25 April, 2008 - Actavis Totowa LLC, a United States manufacturing division of the international generic pharmaceutical company Actavis Group, is initiating a Class 1 nationwide recall of Digitek (digoxin tablets, USP, all strengths) for oral use. The products are distributed by Mylan Pharmaceuticals, Inc. under a "Bertek" label and by UDL Laboratories, Inc. under a "UDL" label.

The voluntary all-lot recall is due to the possibility that tablets with double the appropriate thickness may have been commercially released. These tablets may contain twice the approved level of active ingredient than is appropriate.

Digitek is used to treat heart failure and abnormal heart rhythms. The existence of double-strength tablets poses a risk of digitalis toxicity in patients with renal failure. Digitalis toxicity can cause nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia. Death can also result from excessive Digitalis intake. Several reports of illness and injuries have been received.

Actavis manufactures the products for Mylan and the products are distributed by Mylan and UDL under the Bertek and UDL labels. Bertek and UDL are affiliates of Mylan.

Any customer inquiries related to this action should be addressed to Stericycle customer service at 1-888-276-6166 with representatives' available Monday through Friday, 8 am to 5 pm EST. Additional information about the voluntary recall can also be found at www.actavis.us.

Retailers who have this product are urged to return the product to their place of purchase. If consumers have medical questions, they should contact their health care providers.

This recall is being conducted with the knowledge of the Food and Drug Administration.

Any adverse reactions experienced with the use of this product, and/or quality problems should also be reported to the FDA's MedWatch Program by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, by mail at MedWatch, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787, or on the MedWatch website at www.fda.gov/medwatch.

[58] http://www.actavis.us/en/media+center/newsroom/articles/digitek+recall.htm

Appendix E Press Release - Products Manufactured at Little Falls

Actavis Press Release[59]

02 AUG 2008 / Product

Actavis Totowa Announces Voluntary Recall at the Retail Level of All Drug Products Manufactured at its Little Falls, New Jersey Facility

Morristown, NJ, 1 August, 2008 — Actavis Totowa LLC, a generic drug manufacturer, is announcing a voluntary recall, to the retail level, of all drug products manufactured at its Little Falls, New Jersey facility. This is a precautionary, voluntary action by Actavis following an inspection conducted by the Food and Drug Administration earlier this year.

The inspection at Little Falls revealed operations which did not meet the FDA's or Actavis' standards for good manufacturing practices. Actavis Totowa is voluntarily recalling these products from the pharmacy/retail level, which includes wholesalers and hospitals. The company has informed the FDA regarding this action.

This action is not prompted by product complaints or health hazards associated with the products, which are all prescription medications. Patients who may have these medicines in their possession should continue to take them in accordance with their prescriptions, as the risk of suddenly stopping needed medication may place patients at risk. If patients should wish to obtain replacement medications and/or prescription, they should contact their health care professional or pharmacist. For more information regarding this market action, please visit

http://www.actavis.us/en/media+center/newsroom/articles/RecallFAQ.htm

Recall letters have been issued to wholesalers and retailers, instructing them to return product to Capital Returns, Milwaukee, WI.

Actavis Totowa, LLC is a United States subsidiary of Actavis Group hf. This voluntary action is limited only to the Actavis Totowa products manufactured in the Little Falls, NJ facility listed below. Products manufactured by Actavis Elizabeth LLC, Actavis South Atlantic LLC, Actavis Mid Atlantic LLC or Actavis products manufactured in other facilities are thus not impacted by this recall

The recalled products manufactured at the Little Falls facility are:

Amantadine 100mg capsules	Meperidine & Promethazine capsules
Amibid DM ER tablets	Meperidine HCl 100 mg and 50 mg tablets
Amibid DM tablets	Methenamine Mandelate 0.5 g and 1.0 g tablets
Amidrine capsules	Mirtazapine 15 mg, 30 mg, and 45 mg tablets

[59] http://www.actavis.us/en/media+center/newsroom/articles/Actavis+Totowa+Recall.htm

Amigesic 500 mg caplets and 750 mg caplets	Mirtazapine OD tablets, 15 mg, 30 mg and 45 mg
Amitex PSE tablets	Multi-ret Folic 500 mg tablets
Bellamine S tablets	Multi-vita-bets 0.5 mg and 1.0 mg FL & FE tablets
Betaxolol 10 mg and 20 mg tablets USP	Multi-vita-bets 0.25 mg, 0.5 mg and 1 mg FL tablets
Buspirone HCL 5 mg, 10 mg, 15 mg and 30mg tablets	Naltrexone 50mg tablets
Carisoprodol & Aspirin tablets	Oxycodone & Acetaminophen 5/500mg capsules
Carisoprodol, Aspirin & Codeine tablets	Oxycodone HCl 5 mg, 15 mg and 30 mg tablets
Carisoprodol 350mg tablets	Oxycodone HCl 5 mg capsules
Chlordiazepoxide w/ Clidinium Bromide capsules	Pentazocine & Acetaminophen tablets
Chlorzoxazone 250mg	Pentazocine & Naloxone tablets
Cilostazol tablets 100mg	Phenazopyridine HCl 100 mg and 200 mg tablets
Choline Magnesium Trisalicylate 500 mg, 750 mg and 1000 mg tablets	Phendimetrazine Tartrate 35mg tablets
Cyclobenzaprine HCL 5 mg and 10 mg	Phentermine HCl 37.5 mg tablets
Dexchlorpheniramine Maleate 4 mg and 6 mg tablets	Phentermine HCl 15 mg, 30 mg and 37.5 mg capsules
Dipyridamole 25 mg, 50mg, and 75 mg tablets	Prenatal Formula 3 tablets
Glyburide 1.5 mg, 3.0 mg and 6.0 mg tablets	Prenatal Plus 27 mg FE tablets
Guaifenesin & Codeine Phosphate tablets	Prenatal Rx tablets
Guaifenesin & Phenylephrine tablets	Quinaretic 10mg/12.5mg, 20 mg/12.5 mg and 20 mg/25 mg tablets
Guanfacine 1.0 mg and 2.0 mg HCl tablets	Rifampin 300mg capsules
Hydrocodone & Homatropine tablets	Sodium FL 0.5 mg and 1.0 mg tablets
Hydromorphone HCl tablets	Tizanidine HCl 2 mg and 4 mg tablets
Hydroxyzine 10 mg, 25 mg and 50 mg tablets	Trimethobenzamide 300mg capsules
Hyoscyamine Sulfate 0.125 mg SL	Trimipramine Maleate 25mg, 50mg, 100mg capsules
Hyoscyamine Sulfate 0.375mg SR tablets	Trivita 1 mg FL tablets
Hyoscyamine Sulfate 0.125 mg (oral) tablets	Ursodiol capsules, 300mg
Isradipine 2.5 mg and 5 mg capsules	Vitacon Forte capsules
Loxapine 5 mg, 10 mg, 25 mg, and 50 mg capsules	Vitaplex Plus tablets
Meclizine Chewable 25 mg tablets	Vitaplex tablets (FC)
Meloxicam 7.5 mg and 15 mg tablets	Yohimbine HCl 5.4 mg tablets

Appendix F – Summary of FDA Observations and Events

Event & Location	Quality System	Facilities & Equipment System	Production System	Laboratory & Control System	Regulatory Requirements
FDA 483 – E. Main St. Little Falls, Dated 12/1/04 **6 Observations** **16 Examples Cited**	- Changes made to records without approval (2) examples	-25% of the manufacturing equipment not qualified (6) examples	-Lack of Cleaning Validation (2) examples -Production documentation is not controlled to prevent unauthorized changes (3) examples	-Unsecure computer records (3) examples	
1. FDA 483 – E. Main St. Little Falls – Dated 2/8/06 P-79 **7 Observations**	- Inadequate investigation of complaints – three (3 examples - Inadequate Complaint Procedure		-Control procedures are not established to validate the performance of manufacturing processes – two (2) examples		- Adverse drug experience (ADE) information has not been reported to the FDA - Adverse drug experiences not investigated - Adverse drug experience information not reviewed - Some ADEs were not reported to the FDA - Procedures not established for post marketing ADEs
2. FDA 483 – E. Main St. Little Falls – Dated 8/10/2006 Exhibit 8 **15 Observations**	QA failed to prevent the release of lots that had significant nonconformances, including: - Incomplete lab data - Batch that failed to meet specification - Batch record deviations - Manufacturing deviations QA filed to detect significant discrepancies in Quality reports and records, five (5) examples include: - Stability testing	-Examples of inadequate equipment preventive maintenance program	-Inadequate validation of the cleaning procedures for manufacturing equipment -Inadequate inprocess testing for four (4) examples -Deviations from production and process control procedures not justified for three (3) examples -Master product and control records are incomplete -Equipment qualification issues -Rejected in-process are not	-Seven (7) different product Quality Testing records were incomplete – Examples: -Changes entered into lab notebooks after it was approved -Original out of specification results for three (3) different products were not recorded -Lab computer system was not validated -Stability Testing Protocol not followed	

EVENT & LOCATION	QUALITY SYSTEM	FACILITIES & EQUIPMENT SYSTEM	PRODUCTION SYSTEM	LABORATORY & CONTROL SYSTEM	REGULATORY REQUIREMENTS
	- Process Validation - Batch record Batch failures not investigated - Stability testing - Lab testing - Active ingredient uniformity of tablets		identified and controlled properly -Inadequate storage practices for chemical raw materials -Chemical raw material handling procedure not followed		
3. Warning Letter – E. Main St. – Little Falls – Dated 8/15/2006 P-229	FDA stated that Actavis: -"Several of the observed deficiencies were long-standing, and there is no indication of how or why the lack of compliance was not identified by your firm" -"why it was allowed to continue for such an extended period of item" -"Does your firm have any insight into this situation"? -Prior response to the FDA does not include details that were discussed during the inspection." -Prior response does not identify the cause of the observed deficiencies with regard to postmarking reporting requirements				
4. FDA 483 – Taft Road – October 2006 **3 Observations**				-Deviations not justified -Test Methods not properly validated -Suitability verification not conducted	
5. Mylan Audit Dated 12/04/06 M-24	-Shortage of qualified personnel	-Dated equipment -Warehouse leaking water -Ventilation system smelled of mildew		-Quality Control Lab congested	
6. Revised Warning Letter – E. Main St. Little Falls - Dated 2/1/2007 P-25	-Summarized the prior observations and emphasized the seriousness of the noncompliant observations -Actavis Corrective Action and is in disagreement: o FDA stated "In fact, we do not agree with assertions in your August 29 and 30, 2006 letter that certain of the observations listed on the FDA 483 are not accurate" o "..we are concerned about the quality of the of drug products that have been released from your facility under the serious lack of cGMP controls found during the inspection." o "Your response provides no assurance that the records and conditions of manufacture and testing of each such lot of drug products released and marketed by our firm will be evaluated to assure that the released drug products have their appropriate, identity, strength, quality, and purity."				
7. FDA 483 – E. Main St. Little Falls – Dated 9/28/2007 P-50			-Approved production and process procedures not followed	-Stability Testing Protocol not followed	-FDA required – Field Alert Report not submitted on time

Event & Location	Quality System	Facilities & Equipment System	Production System	Laboratory & Control System	Regulatory Requirements
8. **FDA 483 – Riverview Drive – Dated 5/20/2008 P-26** **11 Observations** **95 Page Establishment Inspection Report**	-Procedures not followed -Responsibilities not followed -Released products not meeting specifications -Four (4) examples of not investigation products out of specification results -Four (4) examples of inadequate investigation into unexplained discrepancies			-Eleven (11) examples where products did not meet specifications throughout the products' labeled shelf life -Five (5) examples of lab controls do not include scientifically sound test procedures	
9. **Actavis 5/20/2008 Memo to Senior Management – Summarizing the FDA Inspection**	FDA Inspector stated "One person was signing of in multiple location and the batch (this occurred on the Digitek double tablet Investigation – The FDA Inspector considered it a very important Observation – additional review of this Investigation may have stopped the release of the batch FDA inspector stated that "from a Quality Systems standpoint, there was a Total Failure". Issues and needs (from FDA inspector): - Do not fix broken systems – get new systems - (Need) Improved infrastructure - Personnel - (Need) Philosophical Change - Investigations on the (past) 483 still not complete - Health hazards on recalls are delinquent - "Get very nervous when you tell us that you are releasing product using		FDA inspector stated that: -"premature to be releasing product" -"concerned about product still on the market that was made in Little Falls using similar systems that had failed" -"concern about the 48 products with no impurity profile"	-	

EVENT & LOCATION	QUALITY SYSTEMS	FACILITIES & EQUIPMENT SYSTEM	PRODUCTION SYSTEM	LABORATORY & CONTROL SYSTEM	REGULATORY REQUIREMENTS
	current Quality Systems				
10. Consent Decree for Permanent Injunction Exhibit 214	-Inspected the firms facilities in Totowa, Little Falls and Taft Rd a total of eight (8) times. The FDA stated: -"drugs are adulterated" -"Interstate commerce drugs that are misbranded" -Introduce or deliver "new drugs that are neither approved" per regulations -"FDA's five inspections of Actavis Totowa's facilities over the last three years have revealed numerous and recurring violations of the current cGMP requirements for drugs"				

Digitek Recall

Assessment of Pharmacovigilance Systems and Risk Communication

Background, Analysis, and Conclusions

Karen A. Frank, M.D.

June 15, 2010

I. TIMELINE

1956 Actavis Group was founded as privately held company in Reykjavik, Iceland

1983 Amide Pharmaceuticals, Inc. was founded in New Jersey, USA

1992 – 2001 First Consent Decree of Permanent Injunction against Amide Pharmaceuticals

December 17, 1999 The earliest FDA-483 observation of a nonreported 15-day alert report for a serious unexpected adverse event (not for Digitek® (digoxin) Tablets.

2001 Consent Decree of Permanent Injunction was lifted from Amide Pharmaceuticals

May 3, 2002 The first FDA-483 observation of a nonreported 15-day alert report with Digitek® (digoxin) tablets for a case of congestive heart failure, cataract extraction, visual disturbances NOS, fatigue, weakness, anorexia, weight decreased.

March 26, 2003 The second FDA-483 observation for nonreported 15-day alert report with Digitek® (digoxin) tablets for events of generalized weakness, atrial fibrillation, feeling of semi-consciousness, and possible digoxin toxicity.

Inspection 1- Elizabeth, NJ - 11Aug03-14Aug03 Postmarketing Adverse Drug Experience (PADE) inspection was classified NAI.

July 9, 2004 First Amide Investigation report of a Product Complaint of Digitek® (digoxin) "double-thick" tablet.

Inspection 2 - Unknown Month 2005 MHRA Inspection. No report available for review.

October 20, 2005 MHRA observation of lack of active exchange program for non-U.S. sourced ADEs with the U.S. Medical Affairs Department.

July 27, 2005 Actavis Group acquired Amide Pharmaceuticals, Inc.

December 19, 2005 Actavis Group purchased the generic division of Alpharma Pharmaceuticals, inclusive of the Copenhagen, Denmark site (site of ex-U.S. Global Pharmacovigilance)

Inspection 3 - Totowa, NJ 17Jan06 – 08Feb06. Inspection to determine compliance with PADE reporting requirements.

February 8, 2006 FDA-483 observations issued for inspection 17Jan06 - 08Feb06 of Totowa, NJ site.

February 28, 2006 Amide Pharmaceuticals response to FDA-483 issued February 8, 2006.

March 1, 2006 Actavis implements agreement between Amide and MHRA for remediation of global reporting requirements for information exchange between Copenhagen, Denmark site and Elizabeth, NJ Site.

April 2006. The reporting of Adverse Drug Events was moved to the U.S. Medical Affairs group in the Elizabeth, NJ facility.

May 15, 2006 Amide Pharmaceuticals, Inc. was reorganized into Actavis Totowa, LLC.

On June 8, 2006, Actavis Totowa notified the Office of Drug Safety (ODS) of the change of contact information for written and verbal communication pertaining to ANDA/DESI/GRANDFATHER products held by Actavis Totowa LLC for Medical Affairs Related Issues Only. These changes are provided as in June 2006, responsibility for investigating product complaints and medical inquiries, as well as SADRs, was transferred from Actavis Totowa to the Actavis U.S. Medical Affairs Department in Elizabeth, New Jersey.

August 29, 2006. The Quality Systems Improvement Plan (QSIP) was initiated as of QSIP was organized into 17 sections, including Organization, Management Review, Laboratory Controls, Micro/Environmental Monitoring, Investigations, CAP A, Documentation , IT, Change Control, Validation, Training, Incoming Materials, Finished Product Release, Compliance, Audits, Warehouse Distribution, Facilities and Equipment, Manufacturing Technology Transfer and Computer Validation. September 2006 consultants begin to assess key areas.

August 15, 2006. FDA Revised Warning Letter issued based on FDA-483 observations of February 8, 2006 and the company response dated February 28, 2006.

September 06, 2006. Company response to August 15, 2006 FDA Revised Warning Letter of February 28, 2006.

September 11, 2006. Company response to August 15, 2006 FDA Revised Warning Letter February 28, 2006. (not included)

October 18, 2006. Company response to August 15, 2006 FDA Revised Warning Letter February 28, 2006. (not included)

November 01, 2006. Company response to August 15, 2006 FDA Revised Warning Letter February 28, 2006. (not included)

Inspection 4 - Little Falls, NJ 10Jul06 -10Aug06

August 10, 2006 FDA-483 observations for inspection dated 10Jul06 – 10Aug06 of Little Falls, NJ site.

February 01, 2007 FDA Warning Letter for Inspection based on August 10, 2006 FDA-483 observations for inspection dated 10Jul06 – 10Aug06 of Little Falls, NJ site.

June 28, 2008 releases (date unknown) Establishment inspection report based on FDA-483 observations dated August 10, 2006 for inspection from 10Jul06 – 10Aug06 of Little Falls, NJ site.

Inspection 5 - Little Falls, NJ 18Sep06-11Oct06

November 17, 2006 Establishment Inspection Report (EIR) for inspection from 18Sep06 – 11Oct06 of Little Falls, NJ site.

Inspection 6 – Elizabeth, NJ 13Dec06-1/29Jan07 covered the Quality, Production, Laboratory Control, and Materials Systems and was classified VAI.

Inspection 7 - Little Falls, NJ 05Sep07 – 28Sep07

September 28, 2007 FDA-483 issued based on 05Sep07 – 28Sep07

May 7, 2008 release (Date unknown) Establishment Inspection report based on FDA-483 dated September 28, 2007 for inspection of 05Sep07-28Sep07.

End of 2007 Trackwise to be used document and track Deviations, Investigations, Change Controls, Out of Specification Investigations.

Inspection 8 – Elizabeth, NJ 21Feb08 and 3Apr08 covered Fentanyl Transdermal complaints and was Classified VAI.

Inspection 9 -Totowa, NJ 18Mar08 – 20May08

May 20, 2008 FDA Inspection Close Out of inspection 18Mar08 – 20May08.

May 20, 2008 FDA-483 issued based on inspection 18Mar08 – 20May08 of Totowa, NJ site.

May 27, 2008 E-mail distribution of FDA-483 from May 20, 2008 (Phyllis Lambridis, Jacob Harron).

May 28, 2009 release (Date unknown) Establishment Inspection report based on FDA-483 dated May 20, 2008 from inspection 18Mar08 – 20May08 of Totowa, NJ site.

Inspection 10 - Elizabeth, NJ 21Apr08-21May08

May 21, 2008 FDA-483 issued on inspection 18Mar08 – 20May08 of Elizabeth, NJ site.

June 06, 2008 Actavis response to FDA-483 observations dated May 21, 2008.

July 11, 2008 FDA response to Actavis response dated June 06, 2008 regarding FDA-483 observations dated May 21, 2008.

August 15, 2008 Actavis response to FDA response July 11, 2008 regarding FDA-483 observations dated May 21, 2008.

May 23, 2008 DIGITEK® (digoxin) Tablets Package issued.

Inspection 11 - Little Falls, NJ 10Jul08-10Aug08

June 23, 2008 release (Date unknown) Establishment Inspection Report from inspection 10Jul08 - 10Aug08 of Lttle Falls, NJ site

August 14, 2008 e-mail from PAREXEL consultant Michael Falkow regarding review of Digitek® adverse events and quality systems issues.

October 16, 2008 Action Plan for closing all Digoxin related complaints.

November 14, 2008 Permanent Injunction

December 23, 2008 Consent Decree of Permanent Injunction

LEGEND for TIMELINE

RED = Inspections

BLUE=Company corrective actions

BLACK BOLD=Intercurrent correspondence

BLACK Regular=Intercurrent merger activities and other activities

II. BACKGROUND

I have been asked to comment on the systemic issues with the Actavis Product Complaint System and Pharmacovigilance System and any potential impact that these systemic issues may have had on safety signal detection and risk assessment in the Digitek® (digoxin) double-thick tablet case. I was provided a dossier of documents, and supplemental documents were provided upon my request. In addition, I was sent the deposition of Misbah Sherwani and Sarita Thapar. At the end of the evaluation, I was provided the E-mail by Michael Falkow and the Action Plan for closing all Digoxin related complaints, as well as examples of some of the complaint reports.

The basis of this opinion is my experience as an expert level FDA reviewer and my 15 years of experience in clinical research and drug safety within the pharmaceutical and biotech industries. This includes experience with the Drug Safety reorganization at F. Hoffmann-LaRoche, Ltd. Headquarters in Switzerland and as a compliance remediation consultant in drug safety in the United States. I have in-depth knowledge of critical issues with pharmacovigilance systems and hands-on experience with the remediation processes, including single case review, PSUR preparation, safety signal detection, labeling updates, and health hazard assessments.

The Actavis Group was founded in 1956 as a privately held company in Reykjavik, Iceland. The Actavis Group is a large generic pharmaceutical company, with locations in about 40 different countries (Exh. 18). Other U.S. sites include: Morristown, NJ (Corporate Office), Elizabeth, NJ (former Alpharma Purepac site), Windsor, MD (site is planning to close and consolidate with NC site), Lincolnton, NC, and Sunrise, FL (R&D facility). (Ref 14 p. 7)

Actavis Totowa, LLC was previously operated as Amide Pharmaceuticals, Inc., which was founded in 1983. The firm operated under a Consent Decree of Permanent Injunction from 1992 - 2001, when the Consent Decree was lifted. Amide was acquired by Actavis on July 27, 2005. Actavis Totowa LLC is a wholly owned subsidiary of Actavis Group (a privately owned company) in Reykjavik, Iceland. On December 19, 2005, the Actavis Group purchased the generic division of Alpharma Pharmaceuticals, inclusive of the Copenhagen, Denmark site with ex-U.S. Pharmacovigilance. On May 15, 2006,the name was legally changed to Actavis Totowa LLC. (Ref 14 p. 7)

There is little or no information provided from the period of 1956 to the time of the FDA inspection from January 2006-February 2006. There was an FDA inspection of the Postmarketing Adverse Drug Experience (PADE) System in Elizabeth, NJ from 11Aug03-14Aug03, which was classified NAI; no other information was provided with regards to this inspection. The first observation of a Digitek® (digoxin) double thick tablet was made in July 2004 (discussed in detail below). In 2005, there was an MHRA inspection that resulted in an inspection observation on October 20, 2005 of inadequate information transfer on expedited cases between the U.S. affiliate and the E.U. affiliate in Copenhagen Denmark, but no further information is provided with regards to this inspection. A remediation plan for this observation was agreed on with the MHRA and was implemented on March 1, 2006.

From the FDA inspections and the Actavis responses, we know that the earliest observation of an unreported 15-day alert expedited report (not Digitek®) was in 1999 based on an FDA-483 observation from February 2005. FDA also found the first FDA-483 observation for nonreported 15-day alert report with Digitek® (digoxin) on May 3, 2002 for a case of congestive heart failure, cataract extraction, visual disturbances NOS, fatigue, weakness, anorexia, weight decreased. A second FDA-483 observation for nonreported 15-day alert report with Digitek® (digoxin) on March 26, 2003 was made for events of generalized weakness, atrial fibrillation, feeling of semi-consciousness, and possible digoxin toxicity.

III. ANALYSIS & CONCLUSIONS

The first report of a double thick Digitek® (digoxin) Tablet was made on July 9, 2004. Company internal investigation did not identify any systemic issues or define additional batches at risk. No further action was taken at that time. On February 8, 2006, an FDA-483 was presented to Actavis with observations of "Adverse drug experience information has not been reported to FDA. Specifically, the following adverse drug experiences or information regarding serious, unexpected adverse drug experiences were not submitted to FDA. Unsubmitted serious, unexpected 15-day alert experiences, where Amide (the application holder or responsible party) did not submit to FDA." The September 6, 2006 Amide response to the FDA-483 states: "Following the February inspection, we reviewed all files relating to suspected adverse drug reactions ("SADRs"), medical inquiries, and product complaints. In the process, we culled reports of 14 instances (8 ANDA and 6 DESI products) that we classified as ADEs requiring a 15-day alert report, and 94 instances that required inclusion in periodic reports. Following discussions with the Office of Drug Safety, we received permission to file a single summary ADE report, for each of the 46 applications, covering the period from the application's date of approval through March 31, 2006. Thereafter, based upon our correspondence with the Office of Drug Safety, we filed 46 summary reports in which all events are discussed." (Ref. 5 p.2)

An FDA Revised Warning Letter dated August 15, 2006 was written in response to the Amide response from February 28, 2006 to the FDA-483 issued on February 8, 2006. The Revised Warning letter reiterates the serious observations of noncompliance with expedited (15-day alert) reporting of serious, unexpected adverse events, and, in particular, they highlight the cases of Digitek® (digoxin) Tablets that were none submitted. The Warning Letter reiterates the serious findings regarding quality and completeness of the information on the 3500A MedWatch forms and the inadequate follow-up on serious cases. In addition, the FDA Warning Letter states "The specific violations noted in this letter are serious and may be symptomatic of underlying problems. You are responsible for investigating and determining the causes of the violations identified above and preventing recurrence of similar violations. (Ref. 4 p.3)

The FDA inspection observation from May 20, 2008 that there were still unreported cases 15-day alert reports over 2 year after the initial FDA observation on noncompliance with expedited reporting in January and February 2006. In addition, there are implications of the FDA observation that "Mr. Delicato stated that the unreported cases from January and February 2006 would be submitted to FDA; however, Mr. Delicato informed me that they did not have a definitive answer to how for back they would go in reviewing unreported cases. He stated that they would include this information in their written response to the New Jersey District." (Ref 15 p. 8) Additional observations made by consultant Michael Falkow on August 14, 2008 further highlight the persistent quality issues with the Actavis pharmacovigilance and product complaint systems. (Ref 20) These observations, taken in their entirety, provide evidence that the pharmacovigilance system and accompanying quality systems remained inadequate to ensure compliance with regulatory reporting or the requirements of the compliance remediation, from either the MHRA inspection of 2005 or the FDA inspection from the first quarter of 2006.

----------The minutes of the May 20, 2008 Inspection Close-out Meeting and the subsequent Establishment Inspection report based on FDA-483 Inspection Observation dated May 20, 2008 from Inspection of Actavis Elizabeth 21Apr08-21May08 provided a summary of inspection observations on the manufacturing, analytical, and quality systems that resulted in the market distribution of multiple batches of Digitek (digoxin Tablets in which there were likely double-thick tablets that may have been suprapotent for digoxin. No analytical analysis was conducted to determine the dose of active moiety of digoxin in each double-thick tablet and no documented risk assessment of the distributed batches. A key FDA inspection observation from the 18Mar08-20May08 Totowa, NJ inspection was "risk assessments and health hazard evaluations were not conducted by the Quality Unit and changes in formulations were not challenged scientifically or analytically resulting in numerous lots of both over and under formulated product" (Ref 14 p. 20). Thus, evidence of inadequate real-time risk assessments and/or inadequate routine health hazard assessments conducted in association with product complaint investigations over a period of several years, including the period covered by the recall of the double-thick Digitek® (digoxin)

Tablets and most likely over the entire period during which double-thick Digitek® (digoxin) Tablets were observed (i.e., since 2004).

The only health hazard assessment provided for review was dated April 18, 2008 and was prepared in conjunction with the Digitek® (digoxin) Tablets. However, the health hazard assessment of April 18, 2008 does refer to a company internal document with an aggregate review of the safety data on Digitek® (digoxin) Tablets. Based upon US Actavis Medical Affairs' internal review of domestic spontaneously reported adverse events with Digitek® (digoxin) Tablets for the period of January 1, 2005 to March 31, 2008, which does not include the entire period during which double-thick Digitek® (digoxin) Tablets were observed. Eleven (11) adverse events were included in this review, and a pattern of events were not identified for this product related or unrelated to known adverse events. However, this US Actavis Medical Affairs' internal review was not reviewed in detail in the health hazard assessment, nor was it provided for review as part of this evaluation to allow independent confirmation of the conclusions.

It is my opinion based on the evidence provided that there was no adequate system to ensure communication between Product Complaints and Drug safety and to ensure real-time health hazard assessments were performed for all product complaints. In my opinion, an inadequate system for real-time health hazard assessments, either in process definition or in implementation, was a significant factor in the inadequate safety signal detection and inadequate assessment of the need to recall distributed batches of drug in response to product complaints.

Routine aggregate analysis is largely lacking in the Actavis pharmacovigilance system, with FDA observations in 2006 of complete noncompliance with PSURs from 1997-2006 despite an SOP for PSUR preparation and submission that was effective in 2002. As part of the remediation to the 2006 inspection findings, the safety signal analysis was done only for serious, unexpected events: This would not be expected to adequately assess any safety signal for either nonserious/unexpected or serious/nonserious expected events associated with either lack of efficacy or digoxin toxicity with the Digitek® (digoxin) Tablets (e.g., increased incidence or severity of events listed as associated with digoxin toxicity in the Digitek® label). Ongoing quality issues with 3500A MedWatch narrative accuracy and completeness are likely to be reflected in suboptimal coding that would affect the complete capture of cases on query of the Actavis Pharmacovigilance database for aggregate reporting and safety signal detection.

In addition, with the influx of product complaints and adverse events that followed the recall of Digitek® (digoxin) Tablets, there is evidence of inadequate due diligence in attempting to secure information on drug lot numbers and samples for each product complaint precludes assessment of the relationship between the product complaint, the batch, and any adverse events reported. On October 16, 2008 Action Plan for closing all Digoxin related product complaints that were reported in the aftermath of the Digitek® (digoxin) Tablet recall. A the time that the plan was approved, there was a back log of approximately 3000 open complaints related to Digitek® (digoxin) Tablets. This action plan was developed on October 16, 2008 to address issues arising from the Digitek® (digoxin) Tablet Recall dated May 23, 2008. It is my opinion based on reasonable evidence, that this plan is reactive, not proactive. The plan provides a process for the completion of the product complaints, but it does not address an associated quality system to ensure that the product complaints are closed out with adequate completeness and quality. In addition, there is no assessment of the resources needed to complete the closeout of the product complaints in a timely manner. No information is provided on metrics to give assurance of the effectiveness of the system. It is my opinion based on reasonable evidence, that despite improvements in product complaint handling in 2007, there remained an braod system issues system for product complaint handling and pharmacovigilance, inadequate due diligence in obtaining important information such as lot number, insufficient personnel to handle the workload, and inadequate quality systems to ensure the effectiveness of the complaint handling system.

There are multiple underlying systemic issues that contributed to the failure of the Actavis Quality System and the Actavis pharmacovigilance system. There was a notable absence oversight from a centralized Headquarters function in Iceland to track local compliance and exchange of information

between U.S. and E.U. affiliates. In addition, there appears to have been a lack of governance at the local affiliate level for critical business processes such as signal detection, complaint investigation, and health hazard assessments. There was most likely an inadequate expansion of personnel and upgrade of business systems to accommodate the increasing workload generated by the 53 approved ANDA applications in the period from 1997 to 2005. In addition, no information was provided on a post-merger system assessment or post-merger systems integration, and such an assessment would have detected inadequate global systems and centralized governance for the expanded workload of the new globalized company. The repeat FDA-483 inspection observations from May 20, 2008 cites a "total failure" of the quality system and persistent serious compliance violations in the pharmacovigilance system, and these observations are indicative of long-standing systemic problems in the acquisition companies and in the post-merger integrated global systems of Actavis Group.

There is repeated and persistent evidence of longstanding noncompliance with regulatory reporting requirements, inadequate remediation of ineffective systems (particularly for expedited reporting), and absent systems from critical business functions such as safety signal detection and health hazard assessments. It is my opinion that the incomplete and ineffective Actavis Pharmacovigilance System may have contributed to unreliable safety signal detection and health hazard assessment associated with the period of time leading up to the recall of Digitek® (digoxin) Tablets in 2008.

In addition to the events leading up to the recall of Digitek® (digoxin) Tablets in 2008, there were observations that arose from the process of the recall itself. Thus, it is my opinion that there were alterations in the press release to the healthcare providers and the general public that may have decreased the magnitude of the risk communicated to healthcare providers and patients. This occurred in the communication of two separate issues: (1) one on the definition of the patient groups at increased risk and (2) a second on two potential adverse outcomes for the double-thick digoxin tablet. These issues are discussed in sequence, below and on the following pages:

(1) Definition of High-Risk Patient Groups: (1a) Patients with daily dosing and (1b) 1b. Patients with renal insufficiency versus patients with renal failure:

The Health Hazard Assessment by Dr. Jerold Leiken dated 18-Apr-2008 (Ref 18) delineated two subgroups of patients that were at risk of digoxin toxicity if they received double-thick tablets with twice their normal daily dose: "If the tablets contain double the dose (0.250 mg), then it can be expected that digitalis toxicity can occur in individuals taking daily doses or in patients with renal insufficiency." The letter in the recall package to the business-to-business customers (Ref 17), reiterated Dr. Leiken's warning on the two high risk groups: "Depending on the constituency of the tablets, double the dose is taken, it can be expected that digitalis toxicity can occur in individuals taking daily doses or in patients with renal insufficiency."

Regarding communication with healthcare providers and the general public, there were no "Dear Prescriber" or "Dear Patient" letters provided in the Recall Package dated 23-May-2008 or in the dossier provided me for review. Thus, one can assume that the communication to the healthcare community and general public appears to have occurred only through the press release in the Recall Package from 23-May-2008 (Ref 17). The Recall Package included a press release that contained a different statement on the patient groups at high risk for digoxin toxicity: "The existence of double strength tablets poses a risk of digitalis toxicity in patients with renal failure." Thus, in the press release to the general public, there was omission of the high risk group of "individuals on daily dosing" and alteration of the high risk group of "patients with renal insufficiency" to include only "patients with renal failure."

"Renal insufficiency" defines a patient subgroup with insufficient excretion of wastes by the kidneys. "The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) defines chronic kidney disease as either kidney damage or a decreased kidney glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for 3 or more months. Whatever the underlying etiology, the destruction of renal mass with irreversible sclerosis and loss of nephrons leads to a progressive decline in GFR. The different stages of chronic kidney disease form a continuum in time; prior to February 2002, no

uniform classification of the stages of chronic kidney disease existed. At that time, K/DOQI published a classification of the stages of chronic kidney disease (Ref 25), as follows:

- Stage 1: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m^2)
- Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m^2)
- Stage 3: Moderate reduction in GFR (30-59 mL/min/1.73 m^2)
- Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m^2)
- Stage 5: Kidney failure (GFR <15 mL/min/1.73 m^2 or dialysis)"

Specifically, the term "renal failure" is applied only to patients with the Stage 5 chronic renal failure with GFR <15 mL/min/1.73 m^2 or dialysis). Clinically, "renal failure" may be subdivided into either "acute renal failure" or "chronic renal failure," but both subgroups define a more severe degree of renal impairment. Thus, substitution of the term "renal failure" for the term "renal insufficiency" in the press release decreases the size of the at risk group and fails to include patients with lesser degrees of renal impairment that may also be at risk of digoxin toxicity with the double-strength, double-thick digoxin tablets.

(2) Alternative Adverse Clinical Outcomes: (2a) Risk of Overdose (digoxin toxicity, include nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia) versus (2b) Risk of Underdose (exacerbation of the underlying cardiac disease (congestive heart failure and arrhythmia) due to lack of therapeutic efficacy):

The Health Hazard Assessment by Dr. Jerold Leiken dated 18-Apr-2008 (Refs 17, 18) described two potential and disparate risks that could be associated with ingestion of the double-thick tablets with twice their normal daily dose:

"Clinical conclusion: Potential risks to the patient depend upon the constituency of the tablets. If the tablets contain double the dose (0.250 mg), then it can be expected that digitalis toxicity can occur in individuals taking daily doses or in patients with renal insufficiency. Toxicity can include nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia. Death can result from excessive digitalis intake.

"If the increased thickness is due to clinically inert substances, then a decreased amount of digitalis may be absorbed, leading to exacerbation of the underlying cardiac disease (congestive heart failure and arrhythmia) due to lack of therapeutic efficacy." (Ref 17, 18)

The letter in the recall package to the business-to-business customers (Ref 17), reiterated Dr. Leiken's warning on the two potential risks with the double-thick tablet:

"Depending on the constituency of the tablets, double the dose is taken, it can be expected that digitalis toxicity can occur in individuals taking daily doses or in patients with renal insufficiency. Toxicity can cause nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia. Death can result from excessive digitalis intake. If the increased thickness is due to clinically inert substances, then a decreased amount of digitalis may be absorbed, leading to exacerbation of the underlying cardiac disease (congestive heart failure and arrhythmia) due to lack of therapeutic efficacy."

Regarding communication with healthcare providers and the general public, there were no "Dear Prescriber" or "Dear Patient" letters provided in the Recall Package dated 23-May-2008 or in the dossier provided me for review. Thus, one can assume that the communication to the healthcare community and general public appears to have occurred only through the press release in the Recall Package from 23-May-2008 (Ref 17). The Recall Package included a press release that contained a statement on the alternative risks of the double-thick digoxin tablet that was substantially different from the statement made by Dr. Leiken in the health hazard assessment:

"Digitalis toxicity can cause nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia. Death can also result from excessive Digitalis intake. Several reports of illnesses and injuries have been received."

Specifically, the statement "If the increased thickness is due to clinically inert substances, then a decreased amount of digitalis may be absorbed, leading to exacerbation of the underlying cardiac disease (congestive heart failure and arrhythmia) due to lack of therapeutic efficacy" has been omitted from the press release to the general public. Thus, omission of the second potential adverse outcome in the press release decreases the size of the patient group at risk group and fails to include patients at risk for exacerbation of underlying congestive heart failure or underlying cardiac arrhythmias secondary to lack of efficacy of subtherapeutic doses of digoxin.

In summary, there were three alterations of the risk communication in the press release to the healthcare providers and the general public as compared to the Health Hazard assessment and the "Dear customer letter" for the business-to-business customers:

(1)The omission of patients on daily dosing as a group at increased risk for digoxin toxicity with a supratherapeutic double-thick digoxin tablet.

(2) Change of the terminology from "renal insufficiency" to "renal failure" to define the group at increased risk for digoxin toxicity with a supratherapeutic double-thick digoxin tablet.

(3) Omission of the alternative clinical scenario of lack of efficacy and exacerbation of underlying congestive heart failure and/or cardiac arrhythmia with subtherapeutic double-thick digoxin tablets.

It is my opinion that this to the general public and the healthcare community does not adequately communicate the full extent of the health risk, because it alters patient population at risk of digoxin toxicity by (1) omitting the patient population on daily dosing and altering the patient population with impaired renal function to include only those with the advanced stage of renal failure and omit those with lesser disease severity of renal insufficiency. Both of these patient populations were defined as at increased risk in the health hazard assessment by Dr. Leiken dated April 18, 2008. Thus, it is my opinion that this press release to the general public and the healthcare community does not adequately communicate the full extent of the health risk to the entire patient population at risk for lack of efficacy because subtherapeutic dosing.

In summary, it is my opinion that there were multiple systems issues in the pharmacovigilance system, the product complaint system, the company internal communication system, and the company system for external communications that all contributed to inadequate product complaint assessment, inadequate company internal communication between product complaint group and drug safety group, insufficient safety signal detection and safety issue recognition, inadequate real-time hazard assessment, lack of timeliness in corrective actions, and inadequate risk communication during the Digitek® (digoxin) Tablet product recall.

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Ref 1. July 9, 2004 Amide Investigation report: Digitek® (digoxin) "double-thick" tablet

Ref 2. February 8, 2006 FDA-483 Form Inspection Observations issued For Inspection 3 - Totowa, NJ 17Jan06 – 08Feb06.

Ref 3. February 28, 2006 Amide Pharmaceuticals response to FDA-483 Form Inspection Observations issued February 8, 2006.

Ref 4. August 15, 2006 Warning Letter based on company response dated February 28, 2006.

Ref 5. September 06, 2006 Company response to August 15, 2006 Revised Warning Letter.

Ref 6. August 10, 2006 FDA-483 Form Inspection Observations for FDA inspection of 10Jul06 – 10Aug06

Ref 7. February 01, 2007 FDA Warning Letter for Inspection based on August 10, 2006 FDA-483 Form Inspection Observations issued for FDA inspection of 10Jul06 – 10Aug06

Ref 8. June 28, 2008 release date Establishment inspection report based on FDA-483 Form Inspection Observations dated August 10, 2006 issued for FDA inspection of 10Jul06 – 10Aug06

Ref 9. November 17, 2006 EIR for Inspection 18Sep06-11Oct06, Little Falls, NJ

Ref 10. September 28, 2007 FDA-483 Form Inspection Observations issued for FDA inspection of 05Sep07 – 28Sep07 of the Little Falls, NJ site.

Ref 11. May 7, 2008 release (Date unknown) Establishment Inspection report based on FDA-483 Form Inspection Observations dated September 28, 2007 for FDA inspection of 05Sep07-28Sep07.

Ref 12. May 20, 2008 FDA Inspection Close Out of Inspection,18Mar08 – 20May08, Totowa, NJ

Ref 13. May 20, 2008 FDA-483 Form Inspection Observations based on inspection 18Mar08 – 20May08

Ref 14. May 28, 2009 release (Date unknown) Establishment Inspection report based on FDA-483 Form Inspection Observations dated May 20, 2008

Ref 15. May 21, 2008 FDA-483 Form Inspection Observations observation Inspection, 21Apr08-21May08 of the Elizabeth, NJ site.

Ref 16. August 15, 2008 Actavis response to FDA response July 11, 2008 regarding FDA-483 Form Inspection Observations dated May 21, 2008 from FDA Inspection of 21Apr08-21May08 of the Elizabeth, NJ site.

Ref 17. May 23, 2008 Digitek® (digoxin) Tablets RECALL PACKAGE dated 23May2008.

Ref 18. Digitek® (digoxin) Tablets Health Hazard Assessment, Dr. Jerrold Leiken, April 18, 2008 included in Digitek® (digoxin) Tablets RECALL PACKAGE dated 23May2008.

Ref 19. June 23, 2008 release date. Establishment Inspection Report from FDA Inspection of 10Jul08 - 10Aug08 of the Little Falls, NJ site.

Ref 20. August 14, 2008 E-mail from Michael Falkow, PAREXEL consultant, to Misbah Sherwani, Senior Quality Assurance Investigations Manager, regarding review of Digitek® adverse events and quality systems issues. (August 14, 2008 2:07 PM). Bates ACTAV 000308945.

Ref 21. October 16, 2008 Memo from Danielle Cowrie, Actavis employee, to Misbah Sherwani, Senior Quality Assurance Investigations Manager regarding Action Plan for closing all Digoxin related complaints. Bates ACTAV 000655812-000655813.

Ref 22. Institute for Safe Medication Practices QuarterWatch 2008 Quarter 2

Ref 23. National Kidney Foundation. *K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification.* Am J Kidney Dis 39:S1-S266, 2002 (suppl 1).

Digitek Recall

Assessment of Pharmacovigilance Systems and Risk Communication

Supporting Documentation

Karen A. Frank, M.D.

June 15, 2010

TIMELINE

1956 Actavis Group was founded as privately held company in Reykjavik, Iceland

1983 Amide Pharmaceuticals, Inc. was founded in New Jersey, USA

1992 – 2001 First Consent Decree of Permanent Injunction against Amide Pharmaceuticals

December 17, 1999 The earliest FDA-483 observation of a nonreported 15-day alert report for a serious unexpected adverse event (not for Digitek® (digoxin) Tablets.

2001 Consent Decree of Permanent Injunction was lifted from Amide Pharmaceuticals

May 3, 2002 The first FDA-483 observation of a nonreported 15-day alert report with Digitek® (digoxin) tablets for a case of congestive heart failure, cataract extraction, visual disturbances NOS, fatigue, weakness, anorexia, weight decreased.

March 26, 2003 The second FDA-483 observation for nonreported 15-day alert report with Digitek® (digoxin) tablets for events of generalized weakness, atrial fibrillation, feeling of semi-consciousness, and possible digoxin toxicity.

Inspection 1- Elizabeth, NJ - 11Aug03-14Aug03 Postmarketing Adverse Drug Experience (PADE) inspection was classified NAI.

July 9, 2004 First Amide Investigation report of a Product Complaint of Digitek® (digoxin) "double-thick" tablet.

Inspection 2 - Unknown Month 2005 MHRA Inspection. No report available for review.

October 20, 2005 MHRA observation of lack of active exchange program for non-U.S. sourced ADEs with the U.S. Medical Affairs Department.

July 27, 2005 Actavis Group acquired Amide Pharmaceuticals, Inc.

December 19, 2005 Actavis Group purchased the generic division of Alpharma Pharmaceuticals, inclusive of the Copenhagen, Denmark site (site of ex-U.S. Global Pharmacovigilance)

Inspection 3 - Totowa, NJ 17Jan06 – 08Feb06. Inspection to determine compliance with PADE reporting requirements.

February 8, 2006 FDA-483 observations issued for inspection 17Jan06 - 08Feb06 of Totowa, NJ site.

February 28, 2006 Amide Pharmaceuticals response to FDA-483 issued February 8, 2006.

March 1, 2006 Actavis implements agreement between Amide and MHRA for remediation of global reporting requirements for information exchange between Copenhagen, Denmark site and Elizabeth, NJ Site.

April 2006. The reporting of Adverse Drug Events was moved to the U.S. Medical Affairs group in the Elizabeth, NJ facility.

May 15, 2006 Amide Pharmaceuticals, Inc. was reorganized into Actavis Totowa, LLC.

On June 8, 2006, Actavis Totowa notified the Office of Drug Safety (ODS) of the change of contact information for written and verbal communication pertaining to ANDA/DESI/GRANDFATHER products held by Actavis Totowa LLC for Medical Affairs Related Issues Only. These changes are provided as in June 2006, responsibility for investigating product complaints and medical inquiries, as well as SADRs, was transferred from Actavis Totowa to the Actavis U.S. Medical Affairs Department in Elizabeth, New Jersey.

August 29, 2006. The Quality Systems Improvement Plan (QSIP) was initiated as of QSIP was organized into 17 sections, including Organization, Management Review, Laboratory Controls, Micro/Environmental Monitoring, Investigations, CAP A, Documentation , IT, Change Control, Validation, Training, Incoming Materials, Finished Product Release, Compliance, Audits, Warehouse Distribution, Facilities and Equipment, Manufacturing Technology Transfer and Computer Validation. September 2006 consultants begin to assess key areas.

August 15, 2006. FDA Revised Warning Letter issued based on FDA-483 observations of February 8, 2006 and the company response dated February 28, 2006.

September 06, 2006. Company response to August 15, 2006 FDA Revised Warning Letter of February 28, 2006.

September 11, 2006. Company response to August 15, 2006 FDA Revised Warning Letter February 28, 2006. (not included)

October 18, 2006. Company response to August 15, 2006 FDA Revised Warning Letter February 28, 2006. (not included)

November 01, 2006. Company response to August 15, 2006 FDA Revised Warning Letter February 28, 2006. (not included)

Inspection 4 - Little Falls, NJ 10Jul06 -10Aug06

August 10, 2006 FDA-483 observations for inspection dated 10Jul06 – 10Aug06 of Little Falls, NJ site.

February 01, 2007 FDA Warning Letter for Inspection based on August 10, 2006 FDA-483 observations for inspection dated 10Jul06 – 10Aug06 of Little Falls, NJ site.

June 28, 2008 releases (date unknown) Establishment inspection report based on FDA-483 observations dated August 10, 2006 for inspection from 10Jul06 – 10Aug06 of Little Falls, NJ site.

Inspection 5 - Little Falls, NJ 18Sep06-11Oct06

November 17, 2006 Establishment Inspection Report (EIR) for inspection from 18Sep06 – 11Oct06 of Little Falls, NJ site.

Inspection 6 – Elizabeth, NJ 13Dec06-1/29Jan07 covered the Quality, Production, Laboratory Control, and Materials Systems and was classified VAI.

Inspection 7 - Little Falls, NJ 05Sep07 – 28Sep07

September 28, 2007 FDA-483 issued based on 05Sep07 – 28Sep07

May 7, 2008 release (Date unknown) Establishment Inspection report based on FDA-483 dated September 28, 2007 for inspection of 05Sep07-28Sep07.

End of 2007 Trackwise to be used document and track Deviations, Investigations, Change Controls, Out of Specification Investigations.

Inspection 8 – Elizabeth, NJ 21Feb08 and 3Apr08 covered Fentanyl Transdermal complaints and was Classified VAI.

Inspection 9 -Totowa, NJ 18Mar08 – 20May08

May 20, 2008 FDA Inspection Close Out of inspection 18Mar08 – 20May08.

May 20, 2008 FDA-483 issued based on inspection 18Mar08 – 20May08 of Totowa, NJ site.

May 27, 2008 E-mail distribution of FDA-483 from May 20, 2008 (Phyllis Lambridis, Jacob Harron).

May 28, 2009 release (Date unknown) Establishment Inspection report based on FDA-483 dated May 20, 2008 from inspection 18Mar08 – 20May08 of Totowa, NJ site.

Inspection 10 - Elizabeth, NJ 21Apr08-21May08

May 21, 2008 FDA-483 issued on inspection 18Mar08 – 20May08 of Elizabeth, NJ site.

June 06, 2008 Actavis response to FDA-483 observations dated May 21, 2008.

July 11, 2008 FDA response to Actavis response dated June 06, 2008 regarding FDA-483 observations dated May 21, 2008.

August 15, 2008 Actavis response to FDA response July 11, 2008 regarding FDA-483 observations dated May 21, 2008.

May 23, 2008 RECALL PACKAGE

Inspection 11 - Little Falls, NJ 10Jul08-10Aug08

June 23, 2008 release (Date unknown) Establishment Inspection Report from inspection 10Jul08 -10Aug08 of Lttle Falls, NJ site

August 14, 2008 e-mail from PAREXEL consultant Michael Falkow regarding review of Digitek® adverse events and quality systems issues.

October 16, 2008 Action Plan for closing all Digoxin related complaints.

November 14, 2008 Permanent Injunction

December 23, 2008 Consent Decree of Permanent Injunction

LEGEND for TIMELINE

RED = Inspections

BLUE=Company corrective actions

BLACK BOLD=Intercurrent correspondence

BLACK Regular=Intercurrent merger activities and other activities

EXPERT OPINIONS on REVIEW of the EVIDENCE

On July 9, 2004, Amide Pharmaceuticals received the first product complaint of a Digitek® (digoxin) Tablet that was thicker than normal. The inspection report is summarized below:

July 9, 2004 Amide Investigation report: Digitek® (digoxin) 0.250 mg Tablet.

"REASON FOR INVESTIGATION

"On 7/7/04 Amide received tablet from a pharmacist at the Rite Aid Pharmacy located at 220 Street Bellingham 98225. The pharmacist indicated that the tablet came from batch 361 Digoxin Tablets 025 mg The tablet has the correct logo 932 standard concave bisect embossed 146 as specified for Digoxin Tablets 0.25 mg. However the tablet is thicker than the normal Digoxin tablet The tablet was measured and found to be 571 mm thick as compared to the thickness specification range of 27 37 mm for Digoxin Tablets 025 mg The tablet was also weighed and was found to weigh 0272 grams as compared to the weight specification range of 0114 0126 grams for Digoxin Tablets 025 mg. (Ref. 1. p. 1)

"LIST OF POSSIBLE CAUSES

"A definitive cause for this very thick tablet was not identified. The mast probable cause was that this was tablet farmed during the initial setup of the compression machine The tablet was not removed from the compression equipment deduster before starting the production run However for purposes of clarity other possible causes that were evaluated during the investigation are included below The thick tablet was farmed during the production run The tablet is actually two tablets stuck together The tablet was not removed from the tablet collection bucket prior to startup. (Ref. 1. p. 1)

"RESULTS OF INVESTIGATION

"The manufacturing batch record for batch 3611A was reviewed The subject batch was compressed on machines 67 and 71 in rooms 119 and 120 on November and 10 2003 There was no indication of any weight or thickness problems during the production run All processing parameters were correctly followed and all test results were within specification Once machine 67 Stokes BB2 was released for startup there were 74 weight checks 740 tablets performed during the production run The tablet weight per 10 average test result was 1207 grams versus specification range of 1176 1224 grams The highest weight per 10 test result was 1220 grams The average tablet thickness result was 316 mm versus specification range of 27 37 mm The thickest tablet result was 325 mm Deduster 123 was used in conjunction with this machine Once machine 71 Stokes Pennwolf was released for startup there were 78weight checks 780 tablets performed during the production run The tablet weight per 10 average test result was 209 grams versus specification range of 1176 224 grams The highest weight per 10 test result was 1222 grams The average tablet thickness result was 318 mm versus specification range of 27 37 mm The thickest tablet result was 324 mm Deduster 124 was used in conjunction with this machine

"The QA inprocess testing results were also reviewed For machines 67 and 71 the combined QA results showed an average tablet weight of 0121 grams 740 tablets tested versus specification range of 0114 0126 grams The average tablet thickness was 320mm 370 tablets tested versus specification range of 2737 mm Again all test results were within specification The tablet was examined to see if it could possibly be two tablets stuck together There was no separation at the tablet midpoint and appeared to be single tablet This is also supported by the design of the compression machines Once tablet is compressed and the machine turntable approaches the tablet discharge location the bottom punch rides up on cam and pushes the tablet up above the surface of the turntable When this occurs the tablet is freed from the turntable and slides toward the discharge chute Should tablet remain stuck to the bottom punch as the

turntable reaches the discharge location the punch slides under scraper arm where the scraper would force the tablet from the punch This would cause the tablet to move to the discharge chute Therefore, there is no possibility of second tablet being compressed on top of the first tablet. The possibility of the very thick tablet being formed during the production run was also discussed For very thick tablet to be formed during production the compression machine would have to be setup incorrectly in either of two ways First the entire machine would have to be setup in such way as to allow the compression of overly thick tablets at all 45 stations review of the inprocess data shows that this did not occur Or second the tooling at single station would have to be incorrectly setup to form overly thick tablets These thick tablets would be produced throughout the production run unless detected by the Production Operators or QA Inspectors No overly thick tablets were seen throughout the run in either the manufacturing or QA inprocess samples There were no comments in the Batch Record related to any weight or thickness issues Also for QA to release the machines for startup tablet from every station is sampled and inspected per the Departmental Operating Instructions If one station had been incorrectly setup to form overly thick tablets the QA inspection would have seen the defect and would have required correction before startup release was given This would prevent any overly thick tablets from being produced during the production run. The concept that tablet remained in the compressed tablet collection bucket and was not rejected prior to the line startup could not be dismissed as possible cause .However, the operators dump the collection buckets into the reject container prior to line startup and it is unlikely that tablet remained in the bucket The corrective action implemented addresses both the tablet remaining in the bucket scenario as well as the tablet remaining in the deduster. (Ref. 1. pp. 2-3)

"CONCLUSION

"The most probable cause for the thick tablet was that this was tablet formed during the initial setup of the compression machine the tablet became stuck in the deduster and the tablet was not removed detected prior to starting the run The current procedure is that the manufacturing operator requests QA startup check once the operator has setup the compression machine to produce tablets within the required specifications When QA confirms that all tablets meet the specifications the equipment is cleared of any setup tablets and the equipment release is given As part of this clearance the deduster vibrator is turned on to show that there are no more tablets in the deduster. The vibrator has normally been operated at slow vibration setting during this step because only small number of tablets have been produced during setup It is believed that the tablet in question was stuck in the tablet deduster vibrator was not dislodged at the slow vibrator setting and was not seen by either Manufacturing or QA prior to the equipment being released for production. (Ref. 1. p. 3)

"CORRECTIVE ACTION

"Production and Quality Assurance Departmental Operating Instructions QAOI PRD084 and PRD085 have been revised to include specific steps for verifying and documenting the clearance of the press deduster and any associated acceptable tablet collection containers Manufacturing operators will clear the dedusters by operating the deduster vibrators at the maximum vibration setting This procedural clarification will apply to all compression equipment and all tablet production Training has been conducted for the Compression Operators Compression Supervisor QA Inspectors and QA Supervisor. (Ref. 1. p. 3)

"DISPOSITION OF INVOLVED BATCHES

"No further action is required for Batch 3611A. The batch will remain in distribution. (Ref. 1. p. 4)

"LIST OF OTHER BATCHES

"This is an isolated incident and is specific to only Batch 3611A No other customer complaints have been received pertaining to this issue. (Ref. 1. p. 4)

SECTION DELETED

"VERIFICATION OF TRAINING

"The employees involved are adequately trained. (Ref. 1. p. 5)

"NEED TO INCLUDE OTHER BATCHES

"Batch 3611A was the first batch in batch campaign. The thick tablet issue was not seen in the inprocess data for any of the batches and has not been seen in any other Customer Complaints. (Ref. 1. p. 5)

"ESTABLISHED PROCEDURES FOLLOWED

"The correct procedures were followed See report. (Ref. 1. p. 5)

SECTION DELETED

"DETERMINATION OF RECURRING PROBLEM

"No previous incidents of this type have been encountered and this is considered to be an isolated incident. (Ref. 1. p. 3)"

COMMENT: No analytical analysis was performed to assess the composition of the tablet for active ingredient or excipients. No accompanying health hazard assessment was provided for to give assurance of safety signal detection from the Amide safety database, regulatory databases, or the literature. No information is provided to indicate that an SOP was in-place and in-use that required routine health hazard assessment for product complaints or other out-of-specification results. No information is provided to allow assessment of the adequacy of the risk assessment for other batches already distributed on the market.

A key inspection observation from the FDA inspection of Totowa NJ site from 18Mar08-20May08 was "risk assessments and health hazard evaluations were not conducted by the Quality Unit and changes in formulations were not challenged scientifically or analytically resulting in numerous lots of both over and under formulated product." (Ref 14 p. 20). No information was provide on any health hazard assessments other than the one prepared by Dr Leiken on April 18, 2008 for the Digitek® (digoxin) Tablets recall on May 23, 2008 (Ref 18). Dr. Leiken cites a company internal document referred to as "US Actavis Medical Affairs' internal review of domestic spontaneously reported adverse events with Digitek® (digoxin) Tablets for the period of January 1, 2005 to March 31, 2008", which does not include the entire period during which double-thick Digitek® (digoxin) Tablets were observed. It is my opinion based on a reasonable degree of evidence that there were no risk assessments or routine health hazard assessments conducted on an ongoing bases over a period of several years, including the period covered by the recall of the double-thick Digitek® (digoxin) Tablets and most likely over the entire period during which double-thick Digitek® (digoxin) Tablets were observed (i.e., since July 2004 or earlier).

From 17Jan06 – 08Feb06, the FDA conducted an inspection on the Totowa, NJ site to determine compliance with PADE reporting requirements. On February 8, 2006, an FDA-483 was issues with observations of deficiencies in the compliance of the PADE Reporting System. Selected FDA-483 inspection observations relevant to the assessment of the impact on the Digitek® case are included below:

"OBSERVATION 1 (Ref. 2, pp. 1-2)

"Adverse drug experience information has not been reported to FDA.

"Specifically, the following adverse drug experiences or information regarding serious, unexpected adverse drug experiences were not submitted to FDA.

"Unsubmitted serious, unexpected 15-day alert experiences, where Amide (the application holder or responsible party) did not submit to FDA, e.g.:

"CASE 00-002 12/17/1999 Phentermine Primary pulmonary hypertension, Valvular heart disease (regurgitation), Neurotoxic injuries (NOS), Neurotoxological disorder

"CASE 02-006 5/312002 Digitek® (digoxin) Tablets Congestive cardiac failure, Cataract extraction, Visual disturbance NOS, Fatigue, Weakness, Anorexia, Weight Decreased

"CASE 03-017 3/28/2003 Digitek® (digoxin) Tablets 0.25 mg Generalized weakness, atrial fibrillation, feeling of semi-consciousness, possible digoxin toxicity

"CASE 04-043 7/23/2004 Phenazopyridine HCl Tablets 200mg Asthenia, Feeling abnormal, Headache, Chest discomfort, Nausea, Feeling jittery, Oedema, peripheral, Hypersensitivity, Rash

"CASE 05-005 1/21/2005 Phentermine HCl Tablets 37.5m Panic attack, Anxiety, Chemical imbalance, Comatose for six months, lost memory

"CASE 05-087 10/5/2005 Phentermine Death from cardiac dysrhythmia, Overdose"

COMMENT: Multiple serious adverse drug experiences were not reported to the FDA as 15-day alert reports. The earliest observation cited in the FDA-483 was on December 17, 1999, but this was not for Digitek® (digoxin). The first digoxin observation with Digitek® (digoxin) was on May 3, 2002 for a case of congestive heart failure, cataract extraction, visual disturbances NOS, fatigue, weakness, anorexia, weight decreased. A second case with Digitek® (digoxin) was 3/26/2003 for events of generalized weakness, atrial fibrillation, feeling of semi-consciousness, and possible digoxin toxicity. The first double thick product complaint from a healthcare provider was dated July 9, 2004. [Reference Obs. 1, above and Amide investigation of Product Complaint, dated July 7, 2004] No information is provided in a complete assessment of the number of unreported cases or the impact of the under-reporting on safety signal detection, but these 2 observations with Digitek® (digoxin) are relevant for signal detection in that they represent possible digoxin toxicity and/or lack of efficacy. It is my opinion based on a reasonable degree of evidence that the noncompliance with 15-day alert reporting most likely impacted the safety signal detection process during this period.

"Unreported or inaccurate information from serious, unexpected 15-day alert reports, as documented on telephone records or in forwarded case information from a contracted affiliate, e.g.:

"CASE 00-015 5/9/2000 Digitek® Tablets (digoxin) 0.25mg / ANDA 40-282. Death in 2.5 hours after ingestion of first tablet. Unreported information: Previous .Condition – Diabetic.

"CASE 01-020 9/7/2001 Digitek® (digoxin) 0.125g Tablets / ANDA 40-282 Feet swelling. Unreported information: Unreported Information: Event reappeared after reintroduction of medication, dehydration, low potassium level, arrhythmia.

"CASE 05-085 9/29/2005 Dexchlorpheniramine Maleate Tablets ER 6mg/ Prescription without an approved application. Dizziness, Hallucination, Fall resulting in 3broken toes and bruised ribs, Overdose, Lack of effect. Unreported Information: Incorrect concomitant medication (Zyrtex reported instead of Zyprexa), Additional suspect medications were identified by the reporter but not listed as suspect medications on the MedWatch Form 3500A; Provided dosages of concomitant medications were not listed, Narrative incorrect in that broken ribs were listed although broken toes were reported, Narrative was summarized and not complete.

"Unreported follow-up information from the patient's doctor regarding the following serious, unexpected adverse drug experience:

"CASE 00-015 5/9/2000 and 7/24/2000 Digitek® Tablets (digoxin) 0.25mg Death in 2.5 hours after ingestion of first tablet. Follow-up information: Allergic to codeine, Cause of death: Arrest."

COMMENT: Unreported or inaccurate information was observed in the ADE information on the MedWatch forms. The first observation for unreported information and unreported follow-up is for a case with Digitek® (digoxin) on May 9, 2000, for a case of death 2.5 hours post ingestion of first dose. A second case of unreported information with Digitek® was observed from September 7, 2001 for a case of a positive rechallenge (recurrence with reintroduction of drug) for events of dehydration, low potassium, and arrhythmia. It is my opinion based on a reasonable degree of evidence that the noncompliance with 15-day alert reporting most likely impacted the safety signal detection process during this period, such that a lack of accurate and complete information precluded a definitive assessment as to the relationship of the events to a supratherapeutic dose of digoxin from a double-thick Digitek® (digoxin) Tablets.

"**OBSERVATION 2** (Ref. 2. p. 3)

"Adverse drug experiences that were the subject of post-marketing 15-day alert reports were not investigated.

"Specifically, there were no follow-up investigations for the following serious, unexpected experiences:

"CASE 01-020 9/7/2001 Digitek® (digoxin) Tablets 0.125 mg Swollen feet. Submitted to FDA. Expected follow-up: Determine resolution of experience, as patient's experience had not resolved at the time of reporting.

"CASE 02-006 5/3/2002 Digitek® (digoxin) Tablet. Congestive cardiac failure, Cataract extraction, Visual disturbance NOS, fatigue, weakness, anorexia, weight decreased. Not submitted to FDA. Expected follow-up: Determine resolution of the experience, as patient's experiences had not resolved at the time of reporting.

"CASE 05-087 10/5/2005 Phentermine. Death from cardiac dysrhythmia, overdose. Not submitted to FDA. Expected follow-up: Determine patient history, concomitant medications, laboratory tests, indication for use."

COMMENT: Incomplete or absent follow-up investigation was observed on serious, unexpected cases, including cases with an outcome of death. The first case noted with Digitek® (digoxin) Tablets was observed from on September 7, 2001 for a case of a positive rechallenge (recurrence with reintroduction of drug) for events of dehydration, low potassium, and arrhythmia. A second observation with Digitek® (digoxin) Tablet from May 3, 2002 was seen with a case of congestive

cardiac failure, cataract extraction, visual disturbance NOS, fatigue, weakness, anorexia, weight decreased. Both of these cases are relevant to the analysis of safety signal for the double-thick Digitek® (digoxin) Tablets, in that they represent possible digoxin toxicity and/or lack of efficacy. It is my opinion based on a reasonable degree of evidence that the noncompliance with 15-day alert reporting most likely impacted the safety signal detection process during this period, such that a lack of adequate follow-up and complete information precluded a definitive assessment as to the relationship of the events to either digoxin toxicity from a supratherapeutic dose in a double-thick Digitek® (digoxin) Tablets or to lack of efficacy from subtherapeutic dosages of digoxin from a double-thick tablet of excipients.

"OBSERVATION 3 (Ref. 2. p. 3)

"Adverse drug experience information obtained or otherwise received from any source was not reviewed, including information from commercial marketing experience and reports in the scientific literature.

"Specifically, incoming adverse drug experiences from spontaneous, clinical trials, and scientific literature are often not reviewed for seriousness *and/or* expectedness. Any adverse experience which the firm submits to FDA is submitted as a 15-day alert expedited report. Additionally, the firm receives published literature on a monthly basis for review, but does not capture serious, unexpected experiences for cases requiring 15-day alert expedited reports, per "Departmental Operating Instructions RA-009, Adverse Drug Experiences (ADE) Reporting to FDA, effective 7/20/2002."

COMMENT: There are observations of inadequate collection and review of potential ADE information, even from commercial sources or the literature. There were no literature searches or literature reports despite an SOP RA-009 in-place effective from July 20, 2002. No information is provided on a quality system to track compliance with this SOP RA-009. This observation has impact for potential under-reporting of adverse events and inadequate signal detection on aggregate data. It is my opinion based on a reasonable degree of evidence that the lack of case capture from the additional sources most likely impacted the safety signal detection process during this period, such events of either digoxin toxicity from a supratherapeutic dose in a double-thick Digitek® (digoxin) Tablets or to lack of efficacy from subtherapeutic dosages of digoxin from a double-thick tablet of excipients were not identified from supplemental sources such as the peer-reviewed medical literature.

"OBSERVATION 4 (Ref. 2. pp. 3-4)

"Individual ADEs which were not reported to FDA in a post marketing 15-day alert have not been included in a periodic safety report.

"Specifically, the firm has never filed a periodic report with FDA. ANDA and NDA approval dates range from 2/28/1997 to 10/24/2005. The firm's procedure, Departmental Operating Instructions RA-009, Adverse Drug Experiences (ADE) Reporting to FDA, effective 7120/2002, requires the submission of periodic reports; Several adverse experiences remained unreported, e.g.:

"CASE -011 3/17/2003 Digitek® Tablets (digoxin) 0.125mg/ ANDA 40-282. Unresolved loss of taste. Non-serious /unexpected.

"CASE 03-035 10/21 /2003 Betaxolol Tablets 10mg/ ANDA 75-541. Tremors, severe nervousness. Non-serious /expected.

"CASE 0-002 1/23/2004 Digitek® Tablets (digoxin) 0.125mg / ANDA 40-282. Frequent bowel movements, fatigue, lightheadedness, paleness, abnormal feeling. Non-serious / unexpected.

"CASE 04-038 8/6/2004 Digitek® Tablets (digoxin) 0.25mg / ANDA 40-282. Appetite decreased, weight loss, tiredness, tremors. Non-serious/ unexpected.

"CASE 04-039 8/10/2004 Phentermine HCl Tablets 37.5 mg/ ANDA 40-190. Drug didn't show up in blood test. Non-serious /unexpected.

"CASE 04-042 8/18/2004 Digitek® tablets (digoxin) 0.25mg / ANDA 40-282. Black tooth deposits. Non-serious / unexpected.

"CASE 04-053 9/20/2004 Digitek® Tablets (digoxin) 0.125mg / ANDA 40-282. Nausea, vomiting, confusion, heart block. Non-serious/ expected.

"CASE 05-045 5/2/2005 Mirtazapine Tablets 30 mg/ ANDA 76-241 Chest pain, increased blood pressure Lack of effect. Non-serious /unexpected.

"CASE 05-096 11/18/2005 Quinapril Tablets /ANDA 76-459 Unresolved dry cough. Non-serious/expected. (Ref. 2. pp. 3-4)

COMMENT: The firm never complied with any requirement for aggregate reporting, either in the form of U.S. Periodic Reports or ICH Period Safety Update Reports) despite SOP RA-009 in-place, but not in-use. The SOP was effective on July 20, 2002, and the FDA-483 observation was made in February 8, 2006 (approximately 3.5 years after the SOP was effective). It is my opinion based on a reasonable degree of evidence that the noncompliance with aggregate reporting requirements indicates that there was no adequate safety signal detection for this period.

COMMENT: Multiple adverse drug experiences were never filed with Health Authorities, even though SOPs were in-place and in-use. No information is provided to give assurance that there was a quality system in-place and in-use to track compliance with 15-day alert reporting timelines and the correct assessment of seriousness and expectedness. All reports listed were nonserious, but were both expected and unexpected. The first observation with Digitek® (digoxin) was made March 17, 2003 for an unresolved loss of taste. In total, the FDA made 5 observations of nonreported cases with Digitek® dating from March 17, 2003 through September 24, 2004. These cases included adverse events that were possible signs of digoxin toxicity such as nausea, confusion, and heart block. No information was provided to give assurance that an analysis of similar events and safety signal detection was performed on these cases at the time of the investigation into the Product complaint of the "double thick" Digitek® (digoxin) Tablet initiated on July 9, 2004. It is my opinion based on a reasonable degree of evidence that the noncompliance with both 15-day alert reporting and aggregate reporting most likely impacted the safety signal detection process during this period, such that a lack of complete cases capture and adequate aggregate analysis precluded a definitive assessment of both safety signal and the relationship of the events to either digoxin toxicity from a supratherapeutic dose in a double-thick Digitek® (digoxin) Tablets or to lack of efficacy from subtherapeutic dosages of digoxin from a double-thick tablet of excipients.

"Further, [in addition to not filing PSURs], there were 17 periodic adverse experiences reported by one nurse in September 2000 were not submitted for atrial fibrillation and lack of effect when taking Digitek® (digoxin) Tablets. The nurse reported that 20 patients were switched to the innovator brand and his/her adverse experiences resolved within three weeks; only 3 reports were submitted." (Ref. 2. p. 4)

COMMENT: In September 2002, a clustering of 20 cases of lack of efficacy with Digitek® (digoxin) Tablets was reported to Amide, but only 3 of these 20 cases were submitted to the Health Authority. These twenty (20) cases were reported with events consistent with lack of efficacy that

resolved when the patients were switched to the innovator brand of digoxin tablets. No information is provided to give assurance that there was due diligence in assessing the relationship to one or more batches of drug. No information is provided to give assurance that all attempts were made to retrieve a sample of the suspect lots for analytical analysis to assess the composition of the tablets for active ingredient or excipients.

A key inspection observation from the FDA inspection of Totowa NJ site from 18Mar08-20May08 was "risk assessments and health hazard evaluations were not conducted by the Quality Unit and changes in formulations were not challenged scientifically or analytically resulting in numerous lots of both over and under formulated product." (Ref 14 p. 20). No information was provide on any health hazard assessments other than the one prepared by Dr Leiken on April 18, 2008 for the Digitek® (digoxin) Tablets recall on May 23, 2008 (Ref 18). Dr. Leiken cites a company internal document referred to as "US Actavis Medical Affairs' internal review of domestic spontaneously reported adverse events with Digitek® (digoxin) Tablets for the period of January 1, 2005 to March 31, 2008", which does not include the entire period during which double-thick Digitek® (digoxin) Tablets were observed. It is my opinion based on a reasonable degree of evidence that there were no risk assessments or routine health hazard assessments conducted on an ongoing bases over a period of several years, including the period covered by the recall of the double-thick Digitek® (digoxin) Tablets and most likely over the entire period during which double-thick Digitek® (digoxin) Tablets were observed (i.e., since July 2004 or earlier). In this inspection finding from 2006, no risk assessment was provided for review to give assurance that the company performed an impact analysis on batches already on the market, and no accompanying health hazard assessment was provided for review to give assurance of safety signal detection from the Amide safety database, the literature or regulatory databases (AERS/WHO).

It is my opinion based on a reasonable degree of evidence that the noncompliance with both 15-day alert reporting and aggregate PSUR reporting most likely impacted the safety signal detection process during this period, such that a lack of complete cases capture and adequate aggregate analysis precluded a definitive assessment of both safety signal and the relationship of the events to either digoxin toxicity from a supratherapeutic dose in a double-thick Digitek® (digoxin) Tablets or to lack of efficacy from subtherapeutic dosages of digoxin from a double-thick tablet of excipients.

"OBSERVATION 5 (Ref 2 pp.4-5)

"Written procedures have not been developed for the evaluation and reporting to FDA of post marketing adverse drug experiences.

"Specifically,

"There is no procedure regarding the initiation of follow-up investigations or serious, unexpected adverse experiences.

"There is no procedure to adequately complete the MedWatch Form 3500A W that the firm never completes Adverse Event Terms, Section G8.

"There is no procedure for a review of MedWatch Forms to assure the accuracy of information reported to FDA. The firm does not conduct reviews of the cases prior to submission, e.g. the information in the `Describe event or problem', Section B5, was often incomplete and `Date received by manufacturer', Section G4, was often inaccurate." (Ref. 2. pp. 4-5)

COMMENT: FDA observation that no SOPs or other written procedures are in-place or in-use for adequate completion of the FDA MedWatch form. No information is provided on a QC review procedure to give assurance of the quality of the FDA MedWatch forms. It is my opinion based on a reasonable degree of evidence that lack of business processes and quality metrics to ensure complete and accurate completion of the 3500A MedWatch form most likely impacted the safety signal

detection process during this period, such that a lack of adequate follow-up and complete information precluded a definitive assessment as to the relationship of the events to either digoxin toxicity from a supratherapeutic dose in a double-thick Digitek® (digoxin) Tablets or to lack of efficacy from subtherapeutic dosages of digoxin from a double-thick tablet of excipients.

COMMENT: FDA observation that there is no procedure in-place or in-use for tracking compliance with 15-day alert expedited reporting timelines. No information is given on any system of metrics to track compliance with reporting timelines. It is my opinion based on a reasonable degree of evidence that the noncompliance with 15-day alert reporting most likely impacted the safety signal detection process during this period, such that a lack of adequate follow-up and complete information precluded a definitive assessment as to the relationship of the events to either digoxin toxicity from a supratherapeutic dose in a double-thick Digitek® (digoxin) Tablets or to lack of efficacy from subtherapeutic dosages of digoxin from a double-thick tablet of excipients.

COMMENT: Failure to investigate consumer complaints observed during inspection. No information is provided to allow assessment of this observation on complaints associated with Digitek® (digoxin) Tablets. It is my opinion based on a reasonable degree of evidence that the failure to promptly and thoroughly investigate consumer complaints most likely impacted the early identification of double-thick Digitek® (digoxin) Tablets issue with subsequent corrective actions.

"OBSERVATION 7 (Ref. 2. p. 6)

"Complaint procedures are deficient in that they do not include provisions that allow for the review and determination of an investigation by the quality control unit.

"Specifically, the firm's complaint handling procedure does not cover the initiation of a formal investigation when necessary, such as multiple complaints for, the same lot of product or confirmed contamination complaints. For example, investigations were not conducted when four complaints were received for cracked Amidrine Capsules, lot 3636A1, or for an intact metal screw, confirmed to be from the firm's packaging equipment, found ' in a bottle of Vitaplex Tablets." (Ref. 2. p. 6)

COMMENT: FDA observation of deficient complaint handling procedures that do not provide for the review and determination of investigation by the quality unit. Specifically, the complaint handling procedure does not cover the initiation or formal investigation when necessary, such as multiple complaints for the same lot of product or confirmed contamination complaints. No information is provided to give assurance that safety signal detection and health hazard assessments are conducted when indicated in conjunction with product complaint investigations.

In May 2008, FDA inspectors stated "no risk assessments or routine health hazard assessments were conducted on an ongoing bases over a period of several years, including the period covered by the recall of the double-thick Digitek® (digoxin) Tablets and most likely over the entire period during which double-thick Digitek® (digoxin) Tablets were observed (i.e., since 2004). The only health hazard assessment provided was prepared on April 18, 2008 in conjunction with the Digitek® (digoxin) Tablets, but it does refer to an aggregate review of the safety data in a "US Actavis Medical Affairs' internal review of domestic spontaneously reported adverse events with Digitek® (digoxin) Tablets for the period of January 1, 2005 to March 31, 2008", which does not include the entire period during which double-thick Digitek® (digoxin) Tablets were observed.

It is my opinion based on a reasonable degree of evidence that inadequate complaint handling procedures most likely impacted the safety signal detection process during this period, such there is no evidence of a business process mandating health hazard assessments by the Actavis drug safety group in real-time association with each investigation of each product complaint.

February 28, 2006 Amide Pharmaceuticals FINAL Response to FDA-483 Form Inspection Observations issued to Amide Pharmaceuticals on February 8, 2006

"Dear Mr. Ellsworth,

"We respectfully submit this letter and its enclosures in response to form FDA-483, Inspectional Observations, presented to Mr. Divya C. Patel, President of Amide Pharmaceutical, Inc. FDA Consumer Safety Officer Ms. Tara R. Gooen submitted the observation to Amide on February 8, 2006. (Ref 3. p.1)

"Before addressing the observation, Amide wishes to express its appreciation to the Consumer Safety Officer, Ms. Gooen, for her courtesy and cooperation during the inspection. The following responses relate to Observations 1 through 5 that concern the Postmarketing' Drug Experiences Reporting System: (Ref 3. p.1)

"Amide has contacted the Office of Drug Safety and based on their recommendation, Amide will review and submit new or amended reports to; previously submitted alert reports from 1999 to 2005. Amide shall send the summarized periodic reports for each product covering the time period of first anniversary date to March 31, 2006. From April 1, 2006 forward, Amide shall follow the FDA guidelines on Periodic report submission based on recommendations from the Office of Drug Safety. (Ref 3. p.1)

"Amide is also preparing a SOP for Triage of Case Information and Management of Adverse Drug Reaction Reports in which the following will be implemented: (Ref 3. p.1)

1. "All ADEs received by Amide will be classified into serious, unexpected or non-serious and expected.
2. "All 3500A forms will be checked for accuracy and completeness by a second person.
3. "All follow-up will be done for ADEs where required.
4. "Literature reviews will be performed and any ADE identified will be reported appropriately.
5. "All ADE 3500A forms will be faxed to FDA.
6. "For all ANDA products, periodic reports will be submitted to FDA's Office of Drug Safety. (Ref 3. p.1)

"**Specific response to each item is listed below:**

"**OBSERVATION 1** (Ref. 3. p. 2)

"Adverse drug experience information has not been reported to FDA.

"Specifically, the following adverse drug experiences or information regarding serious, unexpected adverse drug experiences were not submitted to FDA.

"**Unsubmitted serious, unexpected 15-day alert experiences, where Amide (the application holder or responsible party) did not submit to FDA, e.g.:** (Ref 3. p.3)

"*CASE 00-002 12/17/1999 Phentermine Primary pulmonary hypertension, Valvular heart disease (regurgitation), Neurotoxic injuries (NOS), Neurotoxological disorder*

"*CASE 02-006 5/312002 Digitek® (digoxin) Tablets Congestive cardiac failure, Cataract extraction, Visual disturbance NOS, Fatigue, Weakness, Anorexia, Weight Decreased*

"*CASE 03-017 3/28/2003Digitek® (digoxin) Tablets 0.25 mg Generalized weakness, atrial fibrillation, feeling of semi-consciousness, possible digoxin toxicity*

"*CASE 04-043 7/23/2004 Phenazopyridine HCl Tablets 200mg Asthenia, feeling abnormal, headache, chest discomfort, nausea, feeling jittery, oedema, peripheral, hypersensitivity, rash*

"*CASE 05-005 1/21/2005 Phentermine HCl Tablets 37.5m Panic attack, anxiety, chemical imbalance, comatose for six months, lost memory*

"*CASE 05-087 10/5/2005 Phentermine Death from cardiac dysrhythmia, overdose*

"**Response**: All the above listed cases will be reviewed and submitted as an amended 15 day alert report where required." (Ref 3. p.3)

"**Unreported or inaccurate information from serious, unexpected** 15-day alert **reports, as documented on telephone records or in forwarded case information from a contracted affiliate, e.g.:** (Ref 3. p.3)

"*CASE 00-015 5/912000 Digitek® Tablets (digoxin) 0.25mg / ANDA 40-282. Death in 2.5 hours after ingestion of first tablet. Unreported information: Previous .Condition – Diabetic.*

"*CASE 01-020 9/7/2001 Digitek® (digoxin) 0.125g Tablets / ANDA 40-282 Feet swelling. Unreported information: Unreported Information: Event reappeared after reintroduction of medication, dehydration, low potassium level, arrhythmia.*

"*CASE 05-085 9/29/2005 Dexchlorpheniramine Maleate Tablets ER 6mg/ Prescription without an approved application. Dizziness, Hallucination, Fall resulting in 3broken toes and bruised ribs, Overdose, Lack of effect. Unreported Information: Incorrect concomitant medication (Zyrtex reported instead of Zyprexa), Additional suspect medications were identified by the reporter but not listed as suspect medications on the MedWatch Form 3500A, Provided dosages of concomitant medications were not listed, Narrative incorrect in that broken ribs were listed although broken toes were reported. Narrative was summarized and not complete.*

"**Response**: The source documents will be reviewed against the final MedWatch report by a health care professional for accuracy and completeness prior to submission." (Ref 3. p.3)

"Unreported follow-up information from the patient's doctor regarding the following serious, unexpected adverse drug experience: (Ref 3. p.3)

"*CASE 00-015 5/9/2000 and 7/24/2000 Digitek® Tablets (digoxin) 0.25mg Death in 2.5 hours after ingestion of first tablet. Follow-up information: Allergic to codeine, Cause of death: Arrest.*

"**Response**: The follow up information for the above case will be reviewed and submitted on follow up MedWatch form. The follow up information will be highlighted to differentiate from the initial information." (Ref 3. p.3)

COMMENT: The response only addresses a process of QC against the source document to ensure all information is transferred to the MedWatch. However, the response to the FDA fails to take into account the need for follow-up to obtain further information on the case and the need for a system to track compliance with expedited reporting timelines and with due diligence on follow-up. No information is provided to give assurance that there is a system in-place and in-use to ensure compliance with 15-day alert reporting timelines and/or a system to ensure due diligence in follow-up for critical missing information. In light of the FDA-483 Inspection Observations from May 20, 2008, it is my opinion based on a reasonable degree of evidence that the company response to the inspection findings was not adequate to remediate the noncompliance with expedited reporting or with inadequate quality of the single case reports.

"**OBSERVATION 2** (Ref. 3. p. 4)

"Adverse drug experiences that were the subject of post marketing 15-day alert reports were not investigated. (Ref. 3. p. 4)

"Specifically, there were no follow-up investigations for the following serious, unexpected experiences: (Ref. 3. p. 4)

"CASE 01-020 Digitek® (digoxin)Tablets 0.125 mg Swollen feet. Submitted to FDA. Expected follow-up: Determine resolution of experience, as patient's experience had not resolved at the time of reporting.

"CASE 02-006 5/3/2002 Digitek® (digoxin) Tablet. Congestive cardiac failure, cataract extraction, visual disturbance nos, fatigue, weakness, anorexia, weight decreased. Not submitted to FDA. Expected follow-up: Determine resolution of the experience, as patient's experiences had not resolved at the time of reporting.

"CASE 05-087 10/5/2005 Phentermine. Death from cardiac dysrhythmia, overdose. Not submitted to FDA. Expected follow-up: Determine patient history, concomitant medications, laboratory tests, indication for use.

"**Response**: Amide had sent an inquiry/response to the complaint (ADE). However a follow-up correspondence was not sent to the customer for each of these complaints when additional information requested was not received. (Ref. 3. p. 4)

"Amide will make reasonable efforts to obtain sufficient information for every case in order to complete a FDA Form 3 500A. In the event that the initial information is insufficient, Amide will make the initial contact via two (2) separate phone calls, with at least one (1) phone call to the reporter within two (2) business days. The letter will be sent to the reporter requesting information if the initial contact cannot be made. (Ref. 3. p. 4)

"Amide is preparing the SOPS for Triage of Case Information and Management of Adverse Drug Reaction Reports." (Ref. 3. p. 4)

COMMENT: The response is appropriate in that it summarizes due diligence efforts to be made in follow-up cases. However, the response fails to take into account the need for a system to track compliance with expedited reporting timelines and to track diligence on follow-up. No information is provided to give assurance that there is a system in-place and in-use to ensure compliance with 15-day alert reporting timelines and/or a system to ensure due diligence in follow-up for critical missing information. In light of the FDA-483 Inspection Observations from May 20, 2008, it is my opinion based on a reasonable degree of evidence that the compliance remediation in 2006 was not adequate, either in content or implementation, to remediate the inspection findings of delinquent expedited reporting, inadequate case follow-up, or inadequate quality of the single case reports.

"OBSERVATION 3 (Ref. 3 p. 5)

"Adverse drug experience information obtained or otherwise received from any source was not reviewed, including information from commercial marketing experience and reports in the scientific literature. (Ref. 3 p. 5)

"Specifically, incoming adverse drug experiences from spontaneous, clinical trials, and scientific literature are often not reviewed for seriousness *and/or* expectedness. Any adverse experience which the firm submits to FDA is submitted as a 15-day alert expedited report. Additionally, the firm receives published literature on a monthly basis for review, but does not capture serious, unexpected experiences for cases requiring 15-day alert expedited reports, per Departmental Operating Instructions RA-009, Adverse Drug Experiences (ADE) Reporting to FDA, effective 7/20/2002. (Ref. 3 p. 5)

"**Response**: Literature review will be done on a weekly basis using "Reaction Weekly". The process for the Literature report review will follow a similar guideline as that used for serious / unexpected adverse event reporting. Amide is preparing the SOPs for Triage of Case Information and Management of Adverse Drug Reaction Reports. " (Ref. 3 p.5)

COMMENT: As above, the response is appropriate. However, no information is provided to give assurance that there is a closed loop system in-place and in-use to ensure compliance with 15-day alert reporting timelines, a system to ensure due diligence in follow-up for critical missing information, or collection of information apart from the literature service of "Reaction weekly". In light of the FDA-483 Inspection Observations from May 20, 2008, do not provide contain information on the remediation of this inspection finding.

"OBSERVATION 4 (Ref. 3 p.6)

"Individual ADEs which were not reported to FDA in a post marketing 15-day alert have not been included in a periodic safety report. (Ref. 3 p.6)

"Specifically, the firm has never filed a periodic report with FDA. ANDA and NDA approval dates range from 2/28/1997 to 10/24/2005. The firm's procedure, Departmental Operating Instructions RA-009, Adverse Drug Experiences (ADE) Reporting to FDA, effective 7120/2002, requires the submission of periodic reports; Several adverse experiences remained unreported, e.g.: (Ref. 3 p.6)

"*CASE -011 3/17/2003 Digitek® Tablets (digoxin) 0.125mg/ ANDA 40-282. Unresolved loss of taste. Non-serious /unexpected.*

"*CASE 03-035 10/21 /2003 Betaxolol Tablets 10mg/ ANDA 75-541. Tremors, severe nervousness. Non-serious /expected.*

"*CASE 0-002 1/23/2004 Digitek® Tablets (digoxin) 0.125mg / ANDA 40-282. Frequent bowel movements, fatigue, lightheadedness, paleness, abnormal feeling. Non-serious / unexpected.*

"*CASE 04-038 8/6/2004 Digitek® Tablets (digoxin) 0.25mg / ANDA 40-282. Appetite decreased, weight loss, tiredness, tremors. Non-serious/ unexpected.*

"*CASE 04-039 8/10/2004 Phentermine HCl Tablets 37.5 mg/ ANDA 40-190. Drug didn't show up in blood test. Non-serious /unexpected.*

"*CASE 04-042 8/18/2004 Digitek® tablets (digoxin) 0.25mg / ANDA 40-282. Black tooth deposits. Non-serious / unexpected.*

"*CASE 04-053 9/20/2004 Digitek® Tablets (digoxin) 0.125mg / ANDA 40-282. Nausea, vomiting, confusion, heart block. Non-serious/ expected.*

"*CASE 05-045 5/2/2005 Mirtazapine Tablets 30 mg/ ANDA 76-241 Chest pain, increased blood pressure, lack of effect. Non-serious /unexpected.*

"*CASE 05-096 11/18/2005 Quinapril Tablets /ANDA 76-459 Unresolved dry cough. Non-serious/expected.*

"Further, 17 periodic adverse experiences reported by one nurse in September 2000 were not submitted for atrial fibrillation and lack of effect when taking Digitek® (digoxin) Tablets. The nurse reported that 20 patients were switched to the innovator brand and his/her adverse experiences resolved within three weeks; only 3 reports were submitted. (Ref. 3 p.6)

"**Response**: Amide shall send the summarized periodic reports for each product covering the time period of first anniversary date to March 31, 2006. From April 1, 2006 we will follow the FDA guidelines on Periodic Report Submission. Submits periodic reports to the FDA for each approved ANDA in accordance with the following schedule: (Ref. 3 p.7)

"For the first three (3) years after approval of the ANDA, the periodic report will be submitted quarterly within thirty (30) days of the last day of the reporting quarter, with the beginning of

the first quarter starting on the date of approval of the application or the first of the following month, whichever is closer. (Ref. 3 p.7)

"After the first three (3) years of marketing of an approved product, periodic reports will be submitted annually within sixty (60) days of the anniversary date of approval of the application for the product or the first of the following month, whichever is closer." (Ref. 3 p.7)

COMMENT: The noncompliance with aggregate reporting in the form of PSURs has significant implications for a lack of process for safety signal detection. The response is appropriate, in that it outlines a plan for remediation of delinquent PSURs. However, there is no system in place to address the cases that were not submitted as a 15-day alert report or included in a PSUR (i.e., they were never reported to the FDA. No information is provided to give assurance that there is a system in-place to ensure compliance with 15-day alert reporting timelines and/or a system to ensure due diligence in follow-up for critical missing information and submission of follow-up information on the 15-day alert reporting timeline. In light of the FDA from the May 20, 2008 inspection, it appears that there were expedited cases from January to February 2006 that were still unreported. Thus, it is my opinion based on a reasonable degree of evidence that the compliance remediation in 2006 was not adequate, either in content or implementation, to remediate the inspection findings of delinquent expedited reporting, inadequate case follow-up, or inadequate quality of the single case reports.

COMMENT: There is no response to the FDA observation that 17 cases from the cluster of 20 cases of lack of efficacy with Digitek® (digoxin) were not reported to the FDA. There appears to be both non-compliance with both single case reporting and an absence of signal detection. In addition, there is a no mention of an aggregate analysis for safety signal detection that would include (1) an Analysis of Similar Events (case series) from the Actavis safety database and (2) an assessment of any correlation between the cluster and a given batch of drugs, both of which are an industry standard for an aggregate analysis in a case of a cluster of event. It is my opinion based on a reasonable degree of evidence that the noncompliance with both 15-day alert reporting and aggregate PSUR reporting most likely impacted the safety signal detection process during this period, such that a lack of complete cases capture and adequate aggregate analysis precluded a definitive assessment of both safety signal and the relationship of the events to either digoxin toxicity from a supratherapeutic dose in a double-thick Digitek® (digoxin) Tablets or to lack of efficacy from subtherapeutic dosages of digoxin from a double-thick tablet of excipients.

"OBSERVATION 5 (Ref. 3 p.7)

"Written procedures have not been developed for the evaluation and reporting to FDA of post marketing adverse drug experiences. (Ref. 3 p.7)

"Specifically:

"There is no procedure regarding the initiation of follow-up investigations or serious, unexpected adverse experiences. (Ref. 3 p.7)

"There is no procedure to adequately complete the MedWatch Form 3500A W that the firm never completes Adverse Event Terms, Section G8. (Ref. 3 p.7)

"There is no procedure for a review of MedWatch Forms to assure the accuracy of information reported to FDA. The firm does not conduct reviews of the cases prior to submission, e.g. the information in the `Describe event or problem', Section B5, was often incomplete and `Date received by manufacturer', Section G4, was often inaccurate. (Ref. 3 p.7)

"**Response**: Amide will create comprehensive SOPS for Triage of Case Information and Management of Adverse Drug Reaction Reports. SOPS for Triage of Case Information and

Management of Adverse Drug Reaction Reports will be prepared and circulated by March 15 and the procedures implemented by April 1, 2006." (Ref. 3 p.7)

COMMENT: The response is appropriate in that it summarizes due diligence efforts to be made in creating SOPS for the business processes of case triage, preparation of ADR reports, and case follow-up. However, the response fails to take into account the need for a system to track compliance with expedited reporting timelines and to track due diligence in case follow-up. There is no information provided on a process for case coding, which effects case retrieval from the safety database, aggregate reporting and signal detection. The response does not provide information on an accompanying quality system to track the effectiveness of the new systems to ensure compliance with 15-day alert reporting timelines and other quality issues with the single case reporting and aggregate reporting.

In light of the FDA-483 Inspection Observations from May 20, 2008, it is my opinion based on a reasonable degree of evidence that the compliance remediation in 2006 was not adequate, either in content or implementation, to remediate the inspection findings of delinquent expedited reporting, inadequate case follow-up, or inadequate quality of the single case reports.

"Response related to Observations 6 to 8 in regards to Good Manufacturing Practices.

"OBSERVATION 7 (Ref. 3 p.9)

"Complaint procedures are deficient in that they do not include provisions that allow for the review and determination of an investigation by the quality control unit. (Ref. 3 p.9)

"Specifically, the firm's complaint handling procedure does not cover the initiation of a formal investigation when necessary, such as multiple complaints for, the same lot of product or confirmed contamination complaints. For example, investigations were not conducted when four complaints were received for cracked Amidrine Capsules, lot 3636A1, or for an intact metal screw, confirmed to be from the firm's packaging equipment, found ' in a bottle of Vitaplex Tablets. (Ref. 3 p.9)

"**Response**: Amide is revising its SOP for Handling of Complaints that will allow the review and determination of an investigation by the quality unit. The SOP will be completed by March 15 and implemented by April 1, 2006." (Ref. 3 p.9)

COMMENT: This is an adequate response, provided that the firm complies with the proposed deadline and the revision of the SOP establishes an adequate procedure for the detection, tracking, investigation and health hazard assessment of product complaints. However, as above, there is no information provided on the associated quality system to ensure the effectiveness of the new systems.

On November 17, 2006, an Establishment inspection report from 9/18/06 – 10/11/06 Inspection of Actavis Totowa LLC, Totowa, NJ stated: "Complaints were reviewed during this inspection. No deficiencies were noted." (Ref 9 p.15)

March 1, 2006 Actavis implements agreement between Amide and MHRA for remediation of global reporting requirements for information between Copenhagen, Denmark site and Elizabeth, NJ Site.

April 2006. The reporting of Adverse Drug Events was moved to the Elizabeth, NJ facility.

May 15, 2006 Amide was reorganized into Actavis Totowa LLC.

On June 8, 2006, Actavis Totowa notified the Office of Drug Safety (ODS) of the change of contact information for written and verbal communication pertaining to ANDA/DESI/GRANDFATHER products held by Actavis Totowa LLC for Medical Affairs Related Issues Only. These changes are provided as in June 2006, responsibility for investigating product complaints and medical inquiries, as well as SADRs, was transferred from Actavis Totowa to the Actavis U.S. Medical Affairs Department in Elizabeth, New Jersey.

August 29, 2006. The Quality Systems Improvement Plan (QSIP) was initiated as of QSIP was organized into 17 sections, including Organization, Management Review, Laboratory Controls, Micro/Environmental Monitoring, Investigations, CAP A, Documentation, IT, Change Control, Validation, Training, Incoming Materials, Finished Product Release, Compliance, Audits, Warehouse Distribution, Facilities and Equipment, Manufacturing Technology Transfer and Computer Validation. September 2006 consultants begin to assess key areas.

"On August 15, 2006, the FDA replied with a Warning Letter based to the February 28, 2006 company response to FDA-483 observations from the 10Jan06 – 08Feb06 inspection of Amide Pharmaceuticals, Little Fall, NJ site. The FDA reiterated that "The inspection was conducted to determine your firm's compliance with the postmarketing Adverse Drug Experience (ADE) reporting requirements". (Ref. 4 p.1) In this Warning Letter, the FDA comments on the adequacy of the February 8, 2006 Actavis response to the FDA inspection observations on the FDA-483 form dated February 8, 2006:

SECTION DELETED

1. "Deviations demonstrating your firm's failure to comply with 21 CFR §§ 314.80, 314.98 and 310.305, which were observed during the inspection, include the following: (Ref. 4 p.2)

   "Failure to submit to the Food and Drug Administration (FDA) ADE reports as required by 21 CFR §§ 314.80(c)(1) and 314.98(a) and 310.305(c). Specifically, there were six potentially serious and unexpected events dating back to 1999 for products such as Digoxin that were not reported to FDA.

   "The inspection also found that your firm failed to submit complete and/or accurate information on some 15-day alert reports submitted under §§ 314.80(c)(1), 314.98(a), and 310.305(c)(1). Examples of information that was omitted from the submitted reports include previous conditions of patients, concomitant medication, event recurrence, and follow-up information obtained from patients' physicians.

   "Furthermore, your firm receives published literature on a regular basis, but does not submit to FDA the serious, unexpected cases outlined in the literature as required by 21 CFR 314.80(d) and 314.98(a)." (Ref. 4 p.2)

COMMENT: The FDA Revised Warning Letter was written in response to the Amide response from February 28, 2006 to the FDA-483 issued on February 8, 2006. The Revised Warning letter reiterates the serious observations of noncompliance with expedited (15-day alert) reporting of serious, unexpected adverse events, and, in particular, they highlight the cases of Digitek® (digoxin)

Tablets that were not submitted. The Warning Letter reiterates the serious findings regarding quality and completeness of the information on the 3500A MedWatch forms and the inadequate follow-up on serious cases. In light of the FDA-483 Inspection Observations from May 20, 2008, it is my opinion based on a reasonable degree of evidence that the compliance remediation in 2006 was not adequate, either in content or implementation, to remediate the inspection findings of delinquent expedited reporting, inadequate case follow-up, or inadequate quality of the single case reports. This most likely precluded a definitive assessment as to the relationship of the events to either digoxin toxicity from a supratherapeutic dose in a double-thick Digitek® (digoxin) Tablets or to lack of efficacy from subtherapeutic dosages of digoxin from a double-thick tablet of excipients.

2. "Serious and unexpected ADE reports were not promptly investigated as required by 21 CFR § 314.80(c)(1)(ii) and 314.98(a). Specifically, in two cases where the patients' adverse experiences had not resolved when your firm received the initial reports, and in one case where only minimal case information concerning a fatal adverse event had been initially reported to your firm, there were no follow-up investigations. " (Ref. 4 p.2)

COMMENT: Again, the FDA reiterates the serious problems with the quality and completeness of the information on the FDA MedWatch form for both serious and nonserious events. There is emphasis on the inadequate follow-up of serious cases such as deaths. In light of the FDA-483 Inspection Observations from May 20, 2008, it is my opinion based on a reasonable degree of evidence that the compliance remediation in 2006 was not adequate, either in content or implementation, to remediate the inspection findings of delinquent expedited reporting, inadequate case follow-up, or inadequate quality of the single case reports. This precluded a definitive assessment as to the relationship of the events to either digoxin toxicity from a supratherapeutic dose in a double-thick Digitek® (digoxin) Tablets or to lack of efficacy from subtherapeutic dosages of digoxin from a double-thick tablet of excipients.

"Your firm failed to adequately review ADE information as required by 21 CFR 314.80(b) and 314.98(a). Specifically, data received from all sources, such as spontaneous reports or clinical trials, were not reviewed for seriousness and expectedness. Instead, your firm classified every submitted report as a 15-day alert report. (Ref. 4 p.2)

3. "Your firm has never filed a periodic safety report as required by 21 CFR 314.80(c)(2) and 314.98(a). The inspection found that your firm is not following procedures that were established for filing periodic safety reports. This failure to submit periodic safety reports has resulted in at least twenty-six ADEs which were never reported to FDA. (Ref. 4 p.2)

4. "Procedures for the surveillance, receipt, evaluation, and reporting of adverse events have not been developed as required by 21 CFR 314.80(b), 314.98(a), and 310.305(a). Specifically, your firm lacks procedures regarding follow-up investigations, adequate completion of the MedWatch form (FDA Form 3500A), maintenance of records to assure timely submission of 15-day alert reports, and evaluation of adverse event data for serious outcome and event expectedness. (Ref. 4 p.2)

"Neither the list above nor the examples on the Form FDA-483, List of Inspectional Observations, which was issued to you on February 8, 2006, is intended to be an all-inclusive list of deficiencies at your firm, nor a complete listing of late ADE reports. It is your responsibility to ensure adherence to each requirement of the Act and its regulations. The FDA expects drug firms to establish sufficient mechanisms to assure that all ADEs are recorded, evaluated, and submitted to the FDA within established time frames as outlined under 21 CFR §§ 310.305, 314.98 and 314.80. (Ref. 4 p.3)

"The specific violations noted in this letter are serious and may be symptomatic of underlying problems. You are responsible for investigating and determining the causes of the violations identified above and preventing recurrence of similar violations." (Ref. 4 p.3)

COMMENT: FDA response reiterates the responsibility of the firm to establish systems to ensure adequate quality of reports and compliance with submission timelines, both for single case reporting and for aggregate reporting. The FDA emphasized the responsibility of the drug firm to establish robust business processes to ensure compliance with mandatory ADE reporting. FDA response gives a clear warning that the violations noted are serious and possibly indicative of serious underlying systemic problems, and again emphasizes that the firm is responsible to establish systems to identify and prevent recurrence of the violations. In light of the FDA-483 Inspection Observations from May 20, 2008, it is my opinion based on a reasonable degree of evidence that the compliance remediation in 2006 was not adequate, either in content or implementation, to remediate the inspection findings of delinquent expedited reporting, inadequate case follow-up, or inadequate quality of the single case reports.

COMMENT: In previous communications, the firm did not provided sufficient information give assurance that the FDA-483 from February 8, 2006 was followed by an aggressive compliance remediation program with root cause analysis, CAPA system, revised business processes, and a quality system with metrics to assess the effectiveness of the new systems. Again, repeat inspection from April to May 2008 revealed similar findings for 15-day alert reports, indicative of persistent systemic issues that may have interfered with safety signal detection. It is my opinion based on a reasonable degree of evidence that lack of business processes and quality metrics to ensure complete and accurate completion of the 3500A MedWatch form most likely impacted the safety signal detection process during this period, such that a lack of adequate follow-up and complete information precluded a definitive assessment as to the relationship of the events to either digoxin toxicity from a supratherapeutic dose in a double-thick Digitek® (digoxin) Tablets or to lack of efficacy from subtherapeutic dosages of digoxin from a double-thick tablet of excipients.

"We have received your February 28, 2006 response to the Form FDA-483, and have made it part of our official files. Your response does not include details that were discussed during the inspection. Specifically, you indicated in discussions during the inspection that ADE reporting would be handled by Alpharma because a well-established system already exists at that site, and Alpharma is owned by Actavis, which is your parent firm. The written response does not state this, nor does it include an explanation of how reports received by Amide will be transferred to Alpharma for review and reporting. Documents provided to the investigator during the inspection appear to be for an Actavis Medical Affairs/Drug Safety Group based in Piscataway, NJ, not Alpharma in Elizabeth, NJ. Please clarify reporting responsibilities, actual location of the medical affairs group, transfer logistics, and applicable Alpharma or Actavis procedures." (Ref. 4 p.3)

COMMENT: The FDA indicates that initial company response was without adequate explanation of how reports received by Amide will be transferred to Alpharma for review and processing. However, the FDA response emphasis that the Amide response did not provide sufficient information in regards to an explanation of how reports received by Amide will be transferred to Alpharma for review and reporting. The FDA response also indicated that the documents provided to the inspector were for the Piscataway site and would not provide information on the adequacy of the Pharmacovigilance systems at the Elizabeth, NJ site. As no information is provided to allow assessment of the process of transfer of case, medical review, quality control or compliance with expedited reporting requirements after the transfer to the Elizabeth, NJ site, the FDA requested further information on the organizational structure, the Pharmacovigilance systems, and the transfer procedures.

In light of the FDA-483 Inspection Observations from May 20, 2008, it is my opinion based on a reasonable degree of evidence that the compliance remediation in 2006 was not adequate, either in content or implementation, to remediate the inspection findings of delinquent expedited reporting, inadequate case follow-up, or inadequate quality of the single case reports. It is my opinion based on a reasonable degree of evidence that lack of business processes and quality metrics to ensure complete and accurate completion of the 3500A MedWatch form most likely impacted the safety signal detection process during this period, such that a lack of adequate follow-up and complete information precluded a definitive assessment as to the relationship of the events to either digoxin toxicity from a supratherapeutic dose in a double-thick Digitek® (digoxin) Tablets or to lack of efficacy from subtherapeutic dosages of digoxin from a double-thick tablet of excipients.

> "In addition, your response does not identify the cause of the observed deficiencies with regard to postmarketing reporting requirements. Several of the observed deficiencies were long-standing, and there is no indication of how or why the lack of compliance was not identified by your firm, and why it was allowed to continue for such an extended period of time. Does your firm have any insight into this situation, and are you reviewing all other regulatory requirements applicable to your firm to assure that you are in compliance with those requirements? " (Ref. 4 p.3)

COMMENT: Inspectors reiteration of responsible to further investigate systemic problems. The company response did not provide a root cause analysis for the observed deficiencies in pharmacovigilance and compliance. There was no explanation for why the lack of compliance was not identified and why it was allowed to continue over such a long period of time.

COMMENT: FDA reiterates the FDA-483 observation of serious deficiencies, some of a long-standing nature, in compliance with the single case reporting requirements. The FDA inquires about quality systems to identify problem with the existing systems, to remediate those problems, and to track effectiveness new systems. The firm did not provide information to allow assessment of the remediation plan for the existing pharmacovigilance system, the adequacy of the quality system in assuring compliance in pharmacovigilance and complaint reporting, and the proposed new pharmacovigilance and product complaint systems. In light of the FDA-483 Inspection Observations from May 20, 2008, it is my opinion based on a reasonable degree of evidence that the compliance remediation in 2006 was not adequate, either in content or implementation, to remediate the inspection findings of delinquent expedited reporting, inadequate case follow-up, or inadequate quality of the single case reports.

There is a series of four (4) responses: A letter from September 06, 2006 with the Actavis response to the August 15, 2006 FDA Revised Warning Letter (discussed below); a September 11, 2006 letter with the Actavis response to the August 15, 2006 FDA Revised Warning Letter (not included); an October 18, 2006 letter with the Actavis response to the August 15, 2006 FDA Revised Warning Letter (not included); and a November 1, 2006 letter with an Actavis response to the August 15, 2006 FDA Revised Warning Letter (not included). Thus, the information provided is not sufficient to completely assess the adequacy of the Actavis response to the FDA Revised Warning letter dated August 15, 2009.

The September 06, 2006 with the Actavis response to the August 15, 2006 FDA Revised Warning Letter is discussed in detail, below and on the following pages:

> "We received your letter on August 22, 2006. Although we are disappointed, we understand why the agency concluded that a Warning Letter was warranted. After reviewing our responses to the form FDA-483 presented to us on February 8, 2006, we must acknowledge that we did not provide a comprehensive evaluation of how Amide had administered its Adverse Drug

Experience ("ADE") program from 1999 into February 2006(1) or a full description of the changes made to assure future compliance. This letter supplements our prior responses and addresses your Warning letter reporting from 1999 to February 2006. (Ref 5 p.1)

"We have identified several reasons why ADE handling did not fully conform to applicable requirements before February 2006. As a general proposition, ADE classification, investigation, and reporting were performed pursuant to procedures that were subject to misconstruction, or were misconstrued. The consequences were (1) that ADEs were not reported when the identities of the patients were not known(2) and (2) literature was not searched for ADE information, albeit ADE cases from literature were reported when submitted to the company or otherwise became known(3). (Ref 5 p.1)

1. "Amide Pharmaceuticals, Inc. was acquired by Actavis Group hf. on July 27, 2005.
2. "If complainants responded to company inquiries for additional information, investigations reports were completed to the extent possible. If the complainant did not respond to an inquiry, the investigation was closed. In either event, the company provided a response to the party that filed the complaint.
3. "The Warning letter states that we receive published literature on "a regular basis, but does not submit to FDA the serious, unexpected cases outline in the literature ...." The literature received and reviewed at this site until February 2006 did not encompass medical journals that contain such cases. Rather, the literature received here addressed pharmaceutical manufacturing and pharmacy issues. As discussed below, appropriate literature currently is reviewed for reporting purposes."

COMMENT: The company response to FDA Revised Warning letter regarding the pharmacovigilance systems in place from 1999-2006 by reiterating that "ADE classification, investigation, and reporting were performed pursuant to procedures that were subject to misconstruction, or were misconstrued. The consequences were (1) that ADEs were not reported when the identities of the patients were not known and (2) literature was not searched for ADE information, albeit ADE cases from literature were reported when submitted to the company or otherwise became known." (Ref 5 p.1) While there is a general response of the cause of the problem, the firm does not give assurance that there was a root cause analyses for each of the FDA observations or assessment of the implications for serious systemic problems. The response addresses only the issues with single case reporting and literature reporting. Information is not provided on routine safety signal detection, aggregate reporting, and the interface of product complaint investigations with routine health hazard assessments. No information is provided to address the adequacy of the training of personnel or the plans for retraining, as needed.

"In addition, Amide's Regulatory Affairs Department, which was responsible for ADE handling (as well as all other regulatory submissions to FDA), was a small group whose resources were frequently overtaxed. For example, the department had only two employees in 1999. While the department had grown to six employees by February 2006, it continued to interpret and misapply its procedures as cited in the form FDA-483 observations. In short, an ADE system that did not always conform to regulations had become institutionalized. The company ended the 1999-2006 seven-year span with 53 approved applications. Over this period, we received 102 reports of possible adverse events and, pursuant to our ADE procedures, as then interpreted and applied, we filed 48 15-day alert reports; these reports involved seven products." (Ref. 5 p.2)

COMMENT: The company appropriately response cites inadequate personnel relative to increasing workload as contributory to the inspections observations of noncompliance with reporting requirements. Again, there is no information on why there was no assessment of the adequacy or

training or the need for retraining. In addition, there is no comment on the issue of an inadequate quality system with metrics to track compliance and/or inadequate governance at both the headquarters level and local affiliate level that may have contributed to the underlying systemic issues that lead to the FDA inspection observations. It is my opinion based on reasonable evidence that inadequate personnel staffing and inadequate personnel training contributed substantially to the noncompliance with 15-day alert expedited reporting that was observed at the 2006 PADE inspection and again at the 2008 repeat PADE inspection.

3. "We acknowledge that, during this period, the failings recited in your letter at page 2 are accurate with respect to the six ADEs not reported, failure to file complete information (item 5 in MedWatch forms summarized investigation findings instead of providing all details; and item 8 in the form, i.e., the "adverse event term," was not completed), (4) and in most other respects, which are discussed elsewhere in this response. (Ref. 5 p.2)
4. "We note that the company filed 15-day alert reports for all events, including events identified in product labeling. In that respect, we over-reported events by including everything as serious an unexpected. As a corollary, we failed to file periodic reports based upon the belief that events were already reported. Finally, we note that in annual reports to the various ANDAs, we included a summary of our ADE reporting."

COMMENT: The FDA observation of inconsistent and inadequate completion of the FDA MedWatch has implications for serious systemic issues with the existing pharmacovigilance system, including the safety signal detection. The omission of the "adverse event term" indicates possible problem with the coding of adverse event data, which can affect retrieval of cases from the safety database and the signal detection performed on the aggregate data. The adequacy of the coding determines the ability to completely capture all cases of a particular event on query of the safety database. It is my opinion that the poor narrative and coding quality mostly likely resulted in incomplete retrieval of cases from the Actavis safety database, under estimation of aggregate event rates, and inadequate safety signal detection.

"CORRECTIVE ACTIONS

"Following the February inspection, we reviewed all files relating to suspected adverse drug reactions ("SADRs"), medical inquiries, and product complaints. In the process, we culled reports of 14 instances (8 ANDA and 6 DESI products) that we classified as ADEs requiring a 15-day alert report, and 94 instances that required inclusion in periodic reports. Following discussions with the Office of Drug Safety, we received permission to file a single summary ADE report, for each of the 46 applications, covering the period from the application's date of approval through March 31, 2006. Thereafter, based upon our correspondence with the Office of Drug Safety, we filed 46 summary reports in which all events are discussed. The reports classify events as either ADEs requiring a 15-day alert report or subject to periodic reporting requirements. Of the 102 events addressed in these summaries, 91 remained classified as requiring periodic reports, and 11 previously unreported events were covered in new 15-day alert reports. In each such case, a new original or revised form 3500A also was filed. Although the Office of Drug Safety permitted us to extend summary reporting to April 2006, we were able to finish our reviews before that deadline. Accordingly, the reports we submitted in April extend only to March 31, 2006. (Ref. 5 p.2)

"We have reviewed batch records and related documents involving unexpired batches for which serious and unexpected events were reported. We are pleased to report that the records do not suggest any manufacturing or control issues, and that all such batches met their established, approved specifications." (Ref. 5 p.3)

COMMENT: The response adequately addresses the corrective action for submission of the delinquent 15-day alert expedited reports and delinquent periodic reports in summary reports each with a review period from the approval date through March 31, 2006, including compliance with remediation timelines established by the Office of Drug Safety. This appears to have adequately remediated the noncompliance for single case reporting, but it is not clear that these summary ADE reports are adequate corrective action for the noncompliance in aggregate reporting of PSURs.

In addition, no information is provided to allow complete assessment of the adequacy of aggregate review for safety signal detection and any health hazard associated with distributed batches. In addition, if the safety signal analysis was done only for serious, unexpected events, it would not be expected to adequately assess any safety signal for either (1) nonserious/unexpected or (2) serious/nonserious expected events associated with either lack of efficacy or digoxin toxicity with the Digitek® (digoxin) Tablets (e.g., increased incidence or severity of events listed as associated with digoxin toxicity in the Digitek® (digoxin) Tablets product label). Again, the response contains insufficient information to permit assessment of the effectiveness of the safety signal detection methodology and related health hazard assessments associated with unexpired batches.

It is my opinion based on a reasonable degree of evidence that the limitation of the safety signal detection to include only serious, unexpected 15-day alert reports was inadequate to assess safety signal for digoxin toxicity that would have required analysis of labeled events (both serious and nonserious) associated with digoxin toxicity. In addition, it is my opinion based on a reasonable degree of evidence that the limitation of the safety signal detection to include only serious, unexpected 15-day alert reports was inadequate to assess safety signal for lack of efficacy, in that would have required analysis of labeled events (both serious and nonserious) associated with subtherapeutic digoxin level and exacerbation of the underlying disease of congestive heart failure.

"**PREVENTIVE ACTIONS**

"Pertinent procedures were provided to you by Jasmine Shah on April 4, 2006. On April 3, 2006, responsibility for investigation of SADRs was transferred from Amide to the Actavis Global Medical Affairs Department in Piscataway, New Jersey. Copies of Pharmacovigilance procedures were although Global Medical Affairs handled product complaints and medical inquiries for other Actavis companies and sites. On June 8, 2006, Actavis Totowa notified the Office of Drug Safety (ODS) of the change of contact information for written and verbal communication pertaining to ANDA/DESI/GRANDFATHER products held by Actavis Totowa LLC for Medical Affairs Related Issues Only. (Ref. 5 p.3)

"These changes are provided as in June 2006, responsibility for investigating product complaints and medical inquiries, as well as SADRs, was transferred from Actavis Totowa to the Actavis U.S. Medical Affairs Department in Elizabeth, New Jersey. Newly revised procedures memorializing since April 2006, the U.S. Medical Affairs Department has handled all investigations, classification, and reporting of ADRs. A list of 15-day alert reports on Amide/Actavis Totowa products filed by U.S. Medical Affairs Department is provided as Attachment 11; there were 18 such reports from April 1 through August 8, 2006. A separate list of events classified by the U. S Medical Affairs Department as subject to periodic reporting is provided as Attachment 12; there were 21 such reports between April 1 and August 8, 2006. Actavis Totowa now provides the U .S. Medical Affairs Department copies of documents reflecting SADRs and Medical Inquiries, received and documented, within two business days." (Ref. 5 p.3)

5. "Amide Pharmaceuticals, Inc. was reorganized into Actavis Totowa LLC on May 15, 2006."

COMMENT: The response only states that the responsibility was transferred from Actavis Totowa to Actavis Elizabeth. However, no information is provided to allow the assessment of the adequacy

of the case transfer process from Actavis Totowa, NJ site to Actavis Elizabeth, NJ site or the adequacy of the pharmacovigilance system at the Actavis Elizabeth, NJ site. No information is provided on associated quality system with metrics to allow assessment of effectiveness of the new systems in maintaining compliance with regulatory requirements and timelines. In light of the FDA-483 Inspection Observations from May 20, 2008, it is my opinion based on a reasonable degree of evidence that the compliance remediation in 2006 was not adequate, either in content or implementation, to remediate the inspection findings of delinquent expedited reporting, inadequate case follow-up, or inadequate quality of the single case reports.

> "When a report is received, the information is placed on a case form and assessed (apart from a medical inquiry or a product complaint) as either a periodic or expedited ADE. Once a report has been assessed, it is entered into the Oracle AERS database and assigned a case number by the Medical Affairs Coordinators. ADEs then are processed by the Drug Safety Associates (DSAs), all of whom are health care professionals. They attempt to contact the reporter of the adverse event within two business days from the receipt of the report. Two attempts are made to contact the reporter. When the DSA obtains further information from the reporter, he/site records it on the internal Adverse Event Questionnaire form, and enters the case information into Oracle AERS to create a MedWatch submission. If the attempts to contact the reporter are unsuccessful, the DSA attempts to locate a viable address from an external source and send a letter along with a questionnaire to the reporter. Any additional information received about ADE cases is added to the Oracle AERS database. Thereafter, cases are submitted to FDA according to the case priority." (Ref 5 p.4)

COMMENT: The FDA response to the Amide response to the FDA-483 in February 2006 reiterated the responsibility of the firm to establish systems to ensure adequate quality of reports and compliance with submission timelines, for both single case reporting and aggregate reporting. The company response, above, outlines a system of due diligence in obtaining follow-up information on adverse events. However, there is no system described to ensure the adequacy and correctness of the information obtained by this follow-up procedure.

In previous communications, the firm did not provide information give assurance that the FDA-483 observations from February 8, 2006 were followed by an aggressive compliance remediation program with root cause analysis, CAPA system, revised business processes, and a quality system with metrics to assess the effectiveness of the new systems. FDA reiterates the FDA-483 observation of serious deficiencies, some of a long-standing nature, in compliance with the single case reporting requirements. The FDA inquires about quality systems to identify problem with the existing systems, to remediate those problems, and to track effectiveness new systems. In previous correspondence, the firms did not provide information to allow assessment of the remediation plan for the existing pharmacovigilance system, the adequacy of the quality system in assuring compliance in pharmacovigilance and complaint reporting, and the proposed new pharmacovigilance and product complaint systems. In light of the FDA-483 Inspection Observations from May 20, 2008, it is my opinion based on a reasonable degree of evidence that the compliance remediation in 2006 was not adequate, either in content or implementation, to remediate the inspection findings of delinquent expedited reporting, inadequate case follow-up, or inadequate quality of the single case reports.

Inspection 4 - Little Falls, NJ 10Jul06 -10Aug06

From 10Jul06 – 10Aug06, the FDA conducted an inspection on the Totowa, NJ site. On August, 2006, an FDA-483 form was issued with observations of deficiencies in the compliance of Quality Unit, as well as in manufacturing and in the analytical laboratory. Selected FDA-483 observations relevant to the assessment of the impact on the Digitek® (digoxin) Recall case are included below:

August 10, 2006: FDA-483 observations from 7/10/06 – 8/10/06 Inspection of Actavis Totawa LLC

"OBSERVATION 1 (Ref. 6. p.1)

"The quality unit lacks authority to fully investigate errors that have occurred." (Ref. 6. p.1)

COMMENT: This is documented as an issue for laboratory and manufacturing, but it may represent broader underlying systemic issues with Quality Systems in areas such as Product Complaints and Pharmacovigilance.

"OBSERVATION 5 (Ref 6 p.4)

"No QC process on computer databases: No QC of input, no validation of output or QC output, and no audits of TotalChrom Data Acquisition System." (Ref 6 p.4)

COMMENT: This is documented as an issue for laboratory and manufacturing databases, but it may represent broader issues with databases in areas such as Product Complaints and Pharmacovigilance.

February 01, 2007 FDA Revised Warning Letter for Inspection based on August 10, 2006 FDA-483 observations for inspection dated 10Jul06 – 10Aug06 of Actavis Totowa LLC, Little Falls, NJ

"Significant deficiencies were found in the operations of your firm's quality control unit, and thus there is no assurance that drug products manufactured and released into interstate commerce by your firm have the identity, strength, quality, and purity that they purport to possess. (Ref 7 p.1)

"Multiple instances in which the equality control unit failed to adequately investigate and resolve laboratory deviations and OOS results in products that were ultimately released into interstate commerce. Quality control unit reviewed and approved test data and reports that were inaccurate and incomplete. Laboratory notebooks did not include all raw data generated during testing, and analysts do not always document the preparation and testing of samples in notebooks at the time they are done." (Ref 7. Various)

COMMENT: Although this inspection did not include the pharmacovigilance system, it reiterates earlier finding in the quality and manufacturing systems that directly affect the risk assessment for distributed batches. In addition, these observations may be indicative of broader issues with quality systems, including the interface with product complaint systems and the pharmacovigilance systems.

June 28, 2008 (released date) Establishment inspection report based on FDA-483 observations dated August 10, 2006 for inspection from 10Jul06 – 10Aug06 of Actavis Totowa LLC, Little Falls, NJ

"QUALITY SYSTEMS

"OBSERVATION 1 (Ref 8 p.10-11)

"The quality control unit lacks authority to fully investigate errors that have occurred. No assurance that the Quality Unit can be relied upon to fulfilled its responsibilities that all products released meet the requirements for identity, strength, quality, and purity that they purport to contain. (Ref 8 p.10-11)

"Batches that initially failed to meet release specifications were released into interstate commerce without being fully investigated. All laboratory data is not included either batch records and manufacturing deviations were not always documented. (Ref 8 p.10-11)

"21CFR211.22a: QC unit failed to provide adequate oversight. Reference FDA-483 observation 2-15. Laboratory records are deficient and they do not include a complete record of all data obtained during testing SOP QC-059 Investigations of Out of Specification not consistently. (Ref 8 p.10-11)

"21CFR211.194a4, 21CFR211.110b: Responsibilities and procedures applicable to the quality control unit are not fully followed." (Ref 8 p.10-11)

COMMENT: Again, this inspection did not include pharmacovigilance systems, but it contains observations on the quality systems that directly affect the risk assessment for distributed batches. In addition, these observations may be indicative of broader systemic issues with quality systems, including the interface with product complaint systems and the pharmacovigilance systems. These FDA observations may be indicative of broader systemic issues with the quality systems in areas such as product complaints and pharmacovigilance.

Inspection 5 - Little Falls, NJ 18Sep06-11Oct06

From 18Sep06 – 11Oct06, the FDA conducted an inspection on the Totowa, NJ site to determine compliance with PADE reporting requirements. On November 17, 2006, an FDA-483 was issued with observations relevant to the assessment of the impact on the Digitek® case as included below:

November 17, 2006 Establishment inspection report from 9/18/06 – 10/11/06 Inspection of Actavis Totowa LLC, Totowa, NJ

"GENERAL DISCUSSION WITH MANAGEMENT (Ref 9 p.15)

"Complaints were reviewed during this inspection. No deficiencies were noted."

COMMENT: No inspection observations were found on the sampling of product complaints in this inspection. No information is provided on the scope of the inspector's review to allow assessment of the impact on the Digitek® case. (Ref 9 p.15)

Inspection 6 - Elizabeth (?), NJ 13Dec06 – 29Jan07

From 13Dec06 – 29Jan07, the FDA conducted an inspection on the Elizabeth (?), NJ site that covered the Quality, Production, Laboratory Control, and Materials Systems and was classified VAI. No further information was provided on this inspection. No information was provided on any FDA-483 inspection observations relevant to the assessment of the impact on the Digitek® case.

Inspection 7 - Little Falls, NJ 05Sep07 – 28Sep07

From 13Dec07 – 29Jan07, the FDA conducted an inspection on the Little Falls, NJ site. On September 28, 2007 an FDA-483 form with observations relevant to the assessment of the impact on the Digitek® case.

September 28, 2007 FDA-483 observations from 05Sep07 – 28Sep07 inspection of Actavis, Little Falls, NJ site.

OBSERVATION 1(Ref 10, p.01)

"NDA field alert was not submitted within 3 working days of receipt of information on failure to meet specifications in NDA (i.e., receipt of OSS results for stability testing). (Ref 10, p.01)

"SOP-0033 Investigations of Deviations and SOP-0059 Investigation of OOS and Suspect Results are not followed for initiation of investigations upon detection f a deviation or an OOS observation, and investigations are not completed within the 30-day time window. Interim reports are not made where investigations remain open at 30 days." (Ref 10. p. 01)

COMMENT: It is my opinion that these inspection observations of inadequate investigations within an appropriate time frame, including any associated health hazard assessments, indicate increased risk of prolonged market exposure for distributed batches that require the investigations and associated health hazard assessments to trigger a recall. In addition, the FDA was promptly notified of possible defects in distributed batches that could pose a risk to public health.

May 7, 2008 release date. Establishment Inspection report based on FDA-483 dated September 28, 2007 for inspection of 05Sep07-28Sep07.

"The reporting of Adverse Drug Events has been moved to the Elizabeth facility as of April 2006. (Ref 11 p.9) Corrections to the previous PADE inspection will be verified under the next assignment for the Elizabeth facility as all adverse event reporting has been transferred to that facility since the last inspection. (Ref 11. p.1)

"The Quality Systems Improvement Plan (QSIP) was initiated as of August 29, 2006. QSIP was organized into 17 sections, including Organization, Management Review, Laboratory Controls, Micro/Environmental Monitoring, Investigations, CAP A, Documentation, IT, Change Control, Validation, Training, Incoming Materials, Finished Product Release, Compliance, Audits, Warehouse, Distribution, Facilities and Equipment, Manufacturing Technology Transfer and Computer Validation. A copy of the plan was provided and is attached as Exhibit 6. Consultants were utilized beginning in September 2006 in order to assess key areas. (Ref 11. p.9)

"All Standard Operating Procedures (SOPs) and Departmental Operating Instructions (DOIs) have been reviewed and uploaded into QMAS, a validated computer system, which will enable employees to access all procedures and instructions online and will ensure that only the most current revisions of each SOP and DOI is available for reference. Laboratory methods are currently being entered into the QMAS system for the same purpose. (Ref 11. p.9)

"COMPLAINTS (Ref. 10 p.11)

"Complaints were reviewed during the inspection. Prior complaints were not handled in a timely manner. From 6/07-9/07, there was improvement in that complaints were handled in a timely manner. (Ref. 10 p.11)

"QUALITY SYSTEM/OBSERVATION 1 (Ref. 10 p. 18)

"Field alerts not submitted with 3 days of failure of one of distributed batches to meet specification in NDA (i.e. failed stability testing). 21CFR314.81b1ii: Multiple examples p. 18-19." (Ref. 10 p. 18)

COMMENT: In previous communications with the FDA, the firm did not provided sufficient information give assurance that the FDA-483 from February 8, 2006 was followed by an aggressive compliance remediation program with root cause analysis, CAPA system, revised business processes, and a quality system with metrics to assess the effectiveness of the new systems. The FDA reiterated the FDA-483 observation of serious deficiencies, some of a long-standing nature, in compliance with the single case reporting requirements. The FDA inquired about systems to identify problems with the existing systems, to remediate those problems, and to track effectiveness new systems. In previous correspondence, the firm did not provide information to allow assessment of the remediation plan for the existing pharmacovigilance system, the adequacy of the quality system in assuring compliance in pharmacovigilance and complaint reporting, and the proposed new pharmacovigilance and product complaint systems.

The observations in this inspection provide documentation of improvement in compliance with complaint handling. However, the FDA-483 Inspection Observations from May 20, 2008 a reasonable degree of evidence that the compliance remediation of the 2006 inspection findings was not adequate, either in content or implementation, to remediate the inspection findings of delinquent expedited reporting, inadequate case follow-up, or inadequate quality of the single case reports.

"OBSERVATION 3 (Ref 11 p. 20)

"Timeliness of investigation: Investigations were not promptly initiated nor were they completed within the specified 30-day window. Interim reports were not prepared for investigations open at 30 days." (Ref 11 p. 20)

COMMENT: It is my opinion that these inspection observations of inadequate investigations [of deviations, out-of-specification results, and product complaints] within an appropriate time frame, including any associated health hazard assessments, indicate increased risk of prolonged market exposure for distributed batches that require the investigations and associated health hazard assessments to trigger a recall. No information is provided on risk assessment of other lots that may have been distributed to the market. Thus, these findings are consistent with inadequate risk assessment and inadequate safety signal detection.

VOLUNTARY CORRECTIONS (Ref 11 p. 25)

"QSIP – Quality Systems Improvement Plan – initiated 8/29/06 (Ref 11 p. 25)

COMMENT: No information is on the QSIP to allow assessment of the impact of this remediation plan on any liability arising from the Digitek® case. However, the FDA-483 Inspection Observations from May 20, 2008 a reasonable degree of evidence that the compliance remediation of the 2006 inspection findings was not adequate, either in content or implementation, to remediate the inspection findings of such delinquent expedited reporting and inadequate health hazard assessment.

End of 2007 Trackwise to be used document and track Deviations, Investigations, Change Controls, Out of Specification Investigations.

Inspection 8 – from 21Feb08 to 03Apr08 (Elizabeth, NJ?) covered Fentanyl Transdermal complaints and was Classified VAI.

From 22Feb08 – 03Apr08, the FDA conducted an inspection on the Elizabeth (?), NJ covered Fentanyl Transdermal complaints and was classified VAI. No further information was provided on this inspection. There is no information on any FDA-483 inspection observations relevant to the assessment of the impact on the Digitek® case.

Inspection 9 -Totowa, NJ 18Mar08 – 20May08

From 18Mar08-20May08, the FDA conducted an inspection on the Totowa, NJ site. An FDA-483 form was issued with inspection observations relevant to the assessment of the impact on the Digitek® case. Relevant Sections from the Inspection Close Out Meeting, the FDA-483 observations, and the Establishment Inspection Report are included below:

May 20, 2008 FDA Inspection Closeout on May 20, 2008. Inspection of Totowa, NJ site from 3/18/08 – 5/20/08 .

SECTION DELETED

"Erin also said that from a Quality Systems standpoint, there was "Total Failure". Erin said that although you were very responsive during the audit, for example - by recalling 12 products, there is a need for: 1. Improved Infrastructure, 2. Personnel, and 3. Philosophical Shift.(Ref 11 p. 1)

SECTION DELETED

"The Investigators expressed additional concerns: (Ref 11 p. 2)

1. "Investigations on the 483 have still not been completed. (Ref 11 p. 2)

2. "FDA does not have final copies of recall letters. (Ref 11 p. 2)

3. "Health hazards related to recalls are delinquent. (Ref 11 p. 2)

4. "That you put effective Quality Systems place. (Ref 11 p. 2)

5. "Get very nervous when you us you are releasing product using the current Quality Systems (open issues remain). (Ref 11 p. 2)

SECTION DELETED

8. "Based on the speed that we received documents and the inadequacy the recall process, we are very uncomfortable with you approving products so quickly from Little Falls. (Ref 11 p. 2)

9. "One person was signing off in multiple locations on the batch (this occurred on the Digoxin "double tablet" Investigation). Erin considered this a very important Observation - additional review of this Investigation may have stopped release of the batch) (Ref 11 p. 2)

"Lisa communicated that on April 6, 2008, Actavis knew that product recalls had to be done. Approximately one month passed before the first recall was accomplished. Lisa indicated that the Agency approved the draft letters but did not have the signed copies of the letters. Phyllis stated that she could provide copies of the signed recall letters to the FDA today." (Ref 11 p. 2)

COMMENT: In previous communications with the FDA, the firm did not provide sufficient information give assurance that the FDA-483 from February 8, 2006 was followed by an aggressive compliance remediation program with root cause analysis, CAPA system, revised business processes, and a quality system with metrics to assess the effectiveness of the new systems. In spite of Quality System Improvement Program from August 29, 2006, the FDA inspectors assessed a

"'total failure' of the Quality Systems" at the close of this 2008 inspection. In addition, in spite of serious issue with the quality systems, there was product remaining on the market and products continuing to be released onto the market without adequate evaluation. The recall process was complicated by delays in health hazard assessments, recall letters, communications with FDA, and initiation of the product recall. Again, multiple observations provide reasonable evidence of an inadequate compliance remediation program and the persistence of broad systemic issues precluding efficient risk assessment, accurate safety signal detection, and prompt corrective action.

May 20, 2008 FDA-483 observations from 18Mar08 – 20May08 Inspection of Actavis Totowa LLC, Totowa, NJ site.

"OBSERVATION 1 (Ref 14, p. 1)

"Quality Unit routinely failed to document, investigate and address product quality issues at the time of occurrence, including in-process finished product and stability OOS results. (Ref 14, p. 1)

"No assurance is given that the Quality Unit has the procedures, personnel, or systems to adequately evaluate the quality or validation status of product currently manufactured and released. (Ref 14, p. 1)

"Quality of products on the marketplace was not evaluated despite the confirmed OOS results for newly manufactured products. (Ref 14, p. 1)

"OBSERVATION 2 – (Ref 14, p. 1)

"During the packaging of Digoxin Tablets 0.125mg (Lot # 70924A1), five (5) double thick tablets were observed. (Ref 14, p. 1)

"QA approved a 100% visual inspection of 4.8 million tablets in the lot with a resultant 15 additional double thick tablets. (Ref 14, p. 1)

"QA aware of double thick tablets, but released the batch based on AQL sampling which included visual inspection of 1330 tablets. (Ref 14, p. 1)

"No additional thickness testing or analytical evaluation of the double thick tablets was conducted. (Ref 14, p. 1)

"No Root Cause was determined for the defect, but the lot was released following visual inspection. (Ref 14, p. 1)

"There was no documented evaluation of the 89 lots that remained on the market at the time of the inspection. (Ref 14, p. 1)

SECTION DELETED

"OBSERVATION 6 (Ref 14 p. 8)

"Investigations of unexplained discrepancy and a failure of a batch or any of its components to meet any of its specifications did not extend to other batches of the same product and other dry products that may have been associated with the specific failure or discrepancy. (Ref 14 p. 8)

"Although QA investigations 07-093 on 1/25/08 for double thick Digitek® (digoxin) tablets 0.125 mg, Lot # 70924A1 did not establish a root cause analysis for the defective tablets, the investigation was not expanded to evaluate all finished product lots or strength of digoxin tablets. At the time of the inspection, there were 89 lots on the market within expiry. (Ref 14 p. 8)

"Similar issue of a capping issue attributed to damaged punches and discs, but did not evaluate the impact on the finished products or additional lots, but QA investigations concluded that no other lots were affected. Manufacturing continues. (Ref 14 p. 8)

"QA investigation was late, only examined batches other than OOS batch, and concluded that "Since these are non-ANDA products, and the assay results would fall below the specifications, there is no significant impact as a result of this deviation." (Ref 14 p. 8)

SECTION DELETED

"OBSERVATION 8 (Ref 14 p. 10)

"Written records are not always made of investigations into unexplained discrepancies and the failure of a batch or any of its components to meet specifications. (Ref 14 p. 10)

"Specifically, QA investigations are not documented at the time of occurrence and are not completed in a timely manner as required by SOP-Investigations of Deviations (11/3/06). (Ref 14 p. 10)

SECTION DELETED

"OBSERVATION 9 (Ref 14 p. 12)

"Written production and process control procedures are not followed in the execution of production and process control functions and documented at the time of performance. (Ref 14 p. 12)

"SOP regimen completion of investigations within 20 working days. Extension regimens memo to the file describing the progress and the target completion date (Ref 14 p. 12)

"SOP Revision 12, Investigation of Out of Specification Test Results (07/26/07) does not clearly identify the steps to be taken or samples to be tested by each analyst in an investigation of OOS or suspect test results. (Ref 14 p. 12)

"SOP require filing an FDA field alert within 3 working days after receipt of information (confirmed or unconfirmed) for such issues as stability failures or any other significant chemical, physical or other change in a distributed product. This procedure was not filed in that these alerts were not filed within 3 working days. (Ref 14 p. 12)

"OBSERVATION 10 (Ref 14 p.13)

"Changes to written procedures are not reviewed and approved by the quality control unit. (Ref 14 p.13)

"Changes are not all captured within the within the formal change control system. (Ref 14 p.13)

"Changes that are documented in Work Orders are not reviewed and approved by the Quality Unit. (Ref 14 p.13)

"Documentation for changes within the change control system is required by SOPs, but this justification is lacking in detail with regards to quality. Work orders forms were not reviewed. (Ref 14 p.13)

"The justification for making changes within the change control system is not documented or is incomplete. Justification for the changes is frequently not included on the form." (Ref 14 p.13)

COMMENT: This has implications for the arbitrary decisions to change the company received date on the cases transferred late from Denmark, which lead to a significant inspection observation of noncompliance with 15-day alert reporting timelines.

May 28, 2009 release date ESTABLISHMENT INSPECTION REPORT from May 20, 2008 FDA-483 observations from 18Mar08 – 20May08 Inspection of Actavis Totowa LLC, Totowa, NJ site.

"SUMMARY (Ref 14 p. 1-2)

"Qualifying GMP inspection of a new site (990 Riverview Drive, Totowa, NJ) as per FACTS Assignment 923742, Operation ID 3601487. The inspection provided general coverage. Preapproval coverage was planned but not conducted. Inspectional Coverage was afforded through Compliance Program Guidance Manual 7356.002: Drug Manufacturing and 7356.021, Drug Quality Reporting System NDA Alert Reporting. (Ref 14 p. 1) The 990 Riverview Drive, Totowa, NJ 07512 site was intended for transfer of all manufacturing and testing operations from the existing 101 East .Main Street, Little Falls, NJ 07424 site. SECTION DELETED The initial product for the transfer of manufacturing to the facility was Digoxin Tablets. A list of the batches of Digoxin Tablets manufactured at the Riverview Drive, Totowa, NJ site is provided as Exh. 27. The batches have not been, released or distributed. (Ref 14 p. 15)

"A Warning Letter was issued to Actavis Totowa LLC, Little Falls, in 8/06 for the manufacturing of unapproved new drug products ("DESI") and failure to comply with ADE reporting requirements. A second Warning Letter was issued to Actavis Totowa LLC, Little Falls for cGMP, deficiencies in 1/07 (revised Warning Letter was sent in 2/07 for the addition of charges regarding the manufacturing and marketing of Ergotamine containing drug products). (Ref 14 p. 7)

SECTION DELETED

"This [present] inspection was limited to coverage of the Quality System due to significant cGMP deficiencies including but not limited to out of specification' in-process, finished product and stability results for more than prescription pharmaceutical products; digoxin Tablets, 0.125mg, 101# 70924A2, following visual inspection of the xxx remove "double thick" tablets; failure of the Quality Unit to reject products not meeting specifications, to complete Quality Assurance investigations, to expand investigations to other lots and products, to file NDA Field Alerts within .timeframes, and to respond to out of specification products on the marketplace.(Ref 14 p. 2)

SECTION DELETED

"No additional systems were covered following the documented Quality System failure. No pre-approval coverage was afforded and the firm was notified that withholds of pending applications were recommended. Documentary Samples were collected to demonstrate interstate commerce and cGMP violations. No refusals were documented during the inspection. An FDA-483, Inspectional Observations was issued on 5/20/08 to Robert Wessman, CEO. Mr. Wessman committed to not releasing any products prior to' discussion with FDA, conducting a review of all products remaining on the market, closing open investigations, implementing a new Quality structure, and resuming manufacturing on a product-by-product basis. Commitments to recall finished products from the marketplace were initiated on 419/08 and continued throughout the inspection for such products as Digoxin Tablets, xxxxx (Ref 14 p. 2)

SECTION DELETED

"On 4/9/2008 written commitment was provided by Phyllis Lambridis. Vice President U.S. Quality and Compliance (Exh.12). The letter included xxxxxxx for which the firm planned to initiate a voluntary recall due to issues such as out of specification assay and impurity results on stability and process related issues. The letter also included a plan to stop and remediate numerous products/processes due to the current cGMP findings. Additional recalls were added to the list throughout the inspection based on inspectional findings and Information reviewed by

the firm's hired consultants, PAREXEL. The District was formally notified of a probable Class I recall of Digoxin Tablets, 0.125mg, lot# 70924A2 on 4/17/08. (Ref 14 p. 3) SECTION DELETED "The following DOC samples were collected: Xxxxxx, DOC 467814: Digitek® (Digoxin Tablets,-USP), 0.125 mg, Lot # 71005Al, xxxxxxxxxxxxx (Ref 14 p. 3-4)

SECTION DELETED

"ADDITIONAL MEETINGS WITH MANAGEMENT: (Ref 14 p. 13)

SECTION DELETED

"We stated that due to the numerous cGMP deficiencies identified within the Quality System, there was no assurance of the quality of other products currently manufactured or tested by the site. The products that we evaluated had all been determined to have significant process or method related issues. We stated that a comprehensive evaluation of all processes and methods was needed. We requested any information in support of a quality and risk assessment for the remaining products that were manufactured under the same Quality System and released to the market. No evaluation was provided. (Ref 14 p. 15)

"On 4/23/08, following our discussions, we were contacted by Ms. Lambridis which stated that they had decided to stop distribution of all products until further notice. She said that .they would await the PAREXEL evaluations and notify FDA prior to releasing and distributing any products. A copy of the presentations provided by Mr., Olafsson was provided in a letter dated 4/28/08. (Ref 14 p. 15)

"At that time, the firm did not commit to stopping manufacturing despite the numerous product quality issues identified. We, Investigators Zielny and McCaffery, observed manufacturing continuing on 4/22/08 during a walkthrough of the firm's Little Falls, NJ manufacturing facility. Until 4/23/08, when we questioned the quality of all products, they continued to distribute products for which there were known quality issues with the exception of the "recalled" lots. (Ref 14 p. 15)

"We stated during the meeting on 4/23108 our concern regarding the failure of the Quality Unit to respond to the issues identified in laboratory investigations and the failure of the Quality Unit to address manufacturing deficiencies. Although the firm intended to restructure the quality organization and continue hiring, they had difficulty, hiring as per Ms. Lambridis. We also discussed our significant concern with the release of Digoxin Tablets 0.125 mg, lot# 70924A2, following the findings of "double thick" tablets. The investigation was inconclusive and did not extend to all lots or strengths of Digoxin tablets. (Ref 14 p. 15)

SECTION DELETED

"COMPLAINTS

"Complaints, medical inquiries, and suspect adverse drug event reporting are handled by the firm's Elizabeth, NJ facility and were covered by a separate establishment inspection for drug safety issues that are received directly by the firm's Totowa, NJ facilities are forwarded to the Elizabeth, NJ site and are processed. If investigations are requested at the Totowa facilities they will be requested by the Elizabeth, NJ site dated 1/3/08 (Exh. 34) was reviewed and does not require the initial logging of the complaints, inquiries, or suspect adverse drug events by the Totowa, NJ site prior to forwarding the information to the Elizabeth, NJ site. We discussed the need for accountability of both sites for the information and the criticality of processing adverse drug events within timeframes. Apurva Patel, Managing Director agreed that a log should be established to account for all complaints received directly by the site. He noted that investigations or other follow-up activities requested by Elizabeth, NJ would follow current SOPs." (Ref 14 p. 17)

COMMENT: Despite findings of "total failure" of the Quality System that resulted in product recalls, this inspection did not cover the product complaint system or the Pharmacovigilance system. There were no FDA-483 inspection observations on these systems that were germane to the assessment of the contribution the pharmacovigilance system to any liability associated with the Digitek® (digoxin) Tablet Recall.

"RECALL PROCEDURES

SECTION DELETED "We, investigators McCaffery and Zielny, were notified verbally during the inspection of the commitment to voluntarily recall several of the products for which we had discussed out of specification results or manufacturing problems. Commitments for additional voluntary recalls were made during the inspection based on inspectional findings and findings by the firm's hired consultants, PAREXEL. The formal notifications to the New Jersey District Recall Coordinator were received via e-mail and are summarized in (Att). (Ref 14 p. 18)

"The recalls also included a potential Class I Recall for Digoxin Tablets, 0.125 mg and 0.250 mg, due to findings of "double thick" during the packaging process. The Quality Unit approved the visual inspection of the xxxxxxxxxxx and found additional "double thick" tablets. No root cause was identified and evaluations of other lots or strengths were not conducted for this cardio tonic, narrow therapeutic index drug. The recall included xxxxxxxxxxx. (Ref 14 p. 18)

"At the exit meeting we, Investigators McCaffery and Zielny, informed Robert Wessman, CEO that although they had notified us of the commitment to recall on 4/4/08, for the xxxxx and throughout the inspection for numerous other products, the recall letters were not sent until approximately one month later following our inquiry of the dates the final letters were sent. (Ref 14 p. 18)

"Additionally, despite the 10-day timeframe to provide recall information to the FDA following notification of a voluntary recall, no completed recall packages for any of the recalls had been provided at the time of the exit meeting on 5/20/08. Phyllis Lambridis, Vice President Quality and Compliance U.S. acknowledged the delay. Mr. Wessman: stated that they would provide the information to the Agency by 5/23/08 in a written commitment provided on 5/20/08 following the exit meeting. Only xxx packages were received on 5/23/08. (Ref 14 p. 19)

"On 5/30/08, New Jersey District Recall Coordinator was notified by Ms. Lambridis that some lots were omitted from the original recall letters and a second mailing was sent to the consignees. No additional information about the omissions or the date of the resent letters was available at the time of this report." (Ref 14 p. 19)

COMMENT: Delays in recall procedures only served prolonged market exposure of distributed lots, without adequate health hazard assessments until the final health hazard assessment on April 18, 2008 to be included in the Recall Package dated May 23, 2008. Again, these Inspection Observations from May 20, 2008 provide a reasonable degree of evidence that the compliance remediation of the 2006 inspection findings was not adequate, either in content or implementation, to remediate the inspection findings of such delinquent expedited reporting and inadequate health hazard assessment. In addition, there does not appear to be adequate staffing to meet the workload of the voluntary recall. A separate discussion of the adequacy of the risk communication in the Recall Package is included in a separate safety statement.

"OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE (Ref 14 p. 19)

SECTION DELETED "At the exit meeting on 5/20/08 discussions with management were held prior to the issuance of the FDA-483, Inspectional Observations (Ref 14 p. 19).

"OBSERVATION 1 (Ref 14 p. 19)

"The procedures to the control unit are not fully followed. (Ref 14 p. 19)

"Specifically, the Quality Unit routinely failed to document, investigate and address product quality issues at the time, of occurrence, including in-process, finished product and stability out of specification analytical results. SECTION DELETED At the initiation of the inspection, despite the known product quality Issues including, but not limited to in-process, finished product and numerous stability out of specification results, the Quality Unit failed to document, investigate or address product quality issues. There were no products recalled. The market at the time of inspection despite the out of specification stability results for at least xxx different marketed prescription products. Quality Assurance investigations were not documented and/or not completed, reviewed or approved at the time of the findings. Additionally, decisions for finished product release were not supported by scientific rationale and investigations of deviations were not reviewed by multiple personnel in the Quality Unit for concurrence. SECTION DELETED Risk assessments and health hazard evaluations were not conducted by the Quality Unit and changes in formulations were not challenged scientifically or analytically resulting in numerous lots of both over and under formulated product." (Ref 14 p. 20)

COMMENT: This is a key finding, as the FDA inspectors document that there were "no risk assessments or routine health hazard assessments were conducted on an ongoing bases over a period of several years, including the period covered by the recall of the double-thick Digitek® (digoxin) Tablets and most likely over the entire period during which double-thick Digitek® (digoxin) Tablets were observed (i.e., since 2004). The only health hazard assessment provided for review was dated April 18, 2008 and was prepared in conjunction with the Digitek® (digoxin) Tablets. However, the health hazard assessment of April 18, 2008 does refer to a company internal document with an aggregate review of the safety data on Digitek® (digoxin) Tablets. Based upon US Actavis Medical Affairs' internal review of domestic spontaneously reported adverse events with Digitek® (digoxin) Tablets for the period of January 1, 2005 to March 31, 2008, which does not include the entire period during which double-thick Digitek® (digoxin) Tablets were observed. Eleven (11) adverse events were included in this review, and a pattern of events were not identified for this product related or unrelated to known adverse events. However, this US Actavis Medical Affairs' internal review was not reviewed in detail in the health hazard assessment, nor was it provided for review as part of this evaluation to allow independent confirmation of the conclusions. It is my opinion based on the evidence provided that there was no adequate system or business process to ensure communication between Product Complaints and Drug safety and to ensure real-time health hazard assessments were performed for all product complaints. In my opinion, an inadequate system for real-time health hazard assessments, either in process definition or in implementation, was a significant factor in the inadequate safety signal detection and inadequate assessment of the need to recall distributed batches of drug in response to product complaints.

"Promised corrective actions have addressed specific product quality issues identified on the inspection, but have failed to address the restructuring of the Quality System to prevent further cGMP deficiencies and the other products that were manufactured, analyzed and released by the same failed Quality System. CEO, Robert Wessman was notified of all findings at the FDA-483 exit meeting on 5/20/08. Although the firm had discontinued manufacturing, they had resumed distributing product based on a paper review by their hired consultants. At the time of the exit

meeting, batches were released to market despite the lack of a completed assessment of the firm's systems and previously produced products on the market. (Ref 14 p. 20)

"Mr. Wessman stated that they would discontinue the release of all products until further discussions were held with FDA. Heals reiterated a prior commitment to recall the "DEST' and prescription vitamin products identified during the current inspection due to the lack of impurity testing and approved applications. (Ref 14 p. 21)

SECTION DELETED

"OBSERVATION 2 (Ref 14 p. 21)

"Drug products failing to meet established specifications and quality control criteria were not rejected. (Ref 14 p. 21)

"Specifically, during the packaging of Digoxin Tablets O.125mg, lot# 70924Al" double thick tablets were observed. Quality Assurance approved a 100% visual inspection of the xx million tablet lot which resulted in an additional xx double thick tablets. Although Quality Assurance was aware of the "double thick" tablet findings, the batch was then released based on AQL sampling which included visual inspection of xx tablets. No additional thickness testing or analytical evaluation of the cause of the double thick tablets was conducted. No root cause was determined for the defect; however the lot was released to the market by the Quality Unit on 1/28/08 following the visual inspection. There was no documented evaluation of the approximately xx lots that remained on the market at the time of the inspection. (Ref 14 p. 21)

"Review of xxxxxxxxxxxxxxxxxxxxxxxxxxxx (Exh. 2a1 p.1) revealed' during the packaging of the batch on 11/301 "Two tablets of Digoxin tablets 0.125 mg were found with approximately double the thickness from counter channels during packaging/ filling operation on packaging line xxx. According to the batch record (Exh. 2a2 p. 75) and the investigation, the lead operator observed the "double thick" tablets during the packaging of bucket numbers xx. The xxx and xxx were immediately notified. The operators were then instructed to perform a xx inspection (visual) of tablet from the hopper xxx as well as the two subsequent buckets xxx. One additional "double thick" tablet was found in bucket xx by visual inspection and no thick tablets were observed by visual inspection in bucket xxx. The incident in the batch record notes, inspection was completed on 12/1/07 at about xxx. Only one thick tablet was found front xxx QA supervisor, Aida Ruiz, was contacted and with her permission the production was resumed to complete the packaging run with a watchful eye on the counter (Exh. 2a2, p. 75) The xxx notes, "The remainder of the batch was packaged while operators continuous mai1ual inspection of the tablets as traveled down the bottle filler channels. While inspecting the final bucket, number xx, xx more tablets were identified; bringing the total to xx tablets with double the thickness (Exh.2a1 p. 3). (Ref 14 p. 21)

"As per record, the batch was placed on hold on 12/5/07 (Exh. 2a2 pp. 97-98). The batch record also contained an "Inspection Protocol" which was approved by the xxxxxxxxx (Exh. 2a2 pp. 88-89). The protocol described the following: "This inspection is being performed to ensure that all defect tablets have been removed .from the batch. The type of defect to be inspected for will be reviewed with the inspectors. All tablets that are found to be double the -thickness will be reported and rejected. Upon completion of this protocol, an AQL sample protocol will be written for Quality Assurance to evaluate the xxxx (Exh. 2a2 pp. 88-89). The protocol also noted, "xxxx will be conducted at the Taft Road facility. Since the tablets have already been packaged, the bottles will need to be emptied and the bulk tablets xx inspected. A total of xxx count tablets have been packaged which equates to xxx. The findings were included on the "ON line Production Inspection Form." (Exh. 2a2 p. 93). They indicate that, "xxxx with approx. double the thickness were removed during inspection of the batch. The removed tablets are attached with this protocol." The findings are dated 1/18/08. I, investigator McCaffery, asked

Ms. Lambridis and Scott Tablet, Director Quality Assurance, U.S. Research and Development, (former Director of Quality Assurance at Little Falls, NJ), to see the "double thick" tablets, but was told that they were discarded. No analytical testing or thickness testing was performed on the defective tablets. I discussed the lack of assurance that all tablets with the incorrect thickness and therefore potency were removed due to "visual inspection." I also discussed the firm's attempt to inspect the batch into compliance. The xxx was reviewed and approved by the xxx. He initialed and dated all attachments and pages of the investigation on 1/25/08 (Exh. 2a1 p.2). (Ref 14 p. 22)

"The investigation focused on compression of the product. It included a review of the compression records which revealed a stop of press xxx of compression. The upper and lower punches of the press were removed and cleaned "excessive dust build up on the third day of processing 11/19/07." A new start-up was required following the removal of the punches. It was theorized by the Manufacturing Manager that, "tablets found with double thickness might have been produced during the readjustment at start-up. The possibility that tablets might have gotten stuck in the tablet deduster or metal detector and went unnoticed by the press operator is being considered a possible root cause of the tablets found with double the thickness." (Exh. 2a2 pp. 3-4). I questioned the theory of "double thick" tablets at the time of the restart of xxxx because additional tablets were found in xx near the end of the run and xxxx were found by inspection, but not correlated to a particular time in production. I asked Mr. Talbot if it was typical for an operator to restart a previously set press at "double" the thickness. I also asked if the startup material was the reason for the out of specification tablets, why they were only looking for "double thick" tablets when there might be tablets that varied in thickness. Mr. Talbot agreed that startup material would not be just "double thick tablets" and also noted that an operator would not necessarily start at double the thickness when resettling the tablet press. (Ref 14 p. 22)

"The manufacturing department conducted a batch record review of the xx tablet batch; however, it was the compression of the batch. The product was manufactured using xx tablet pres xxxx. It was noted the batch record that e sampled every xx minutes from each chute of each tablet press and checked for thickness as compared to the product specifications xxxxx (Exh. 2a2 p. 25). The manufacturing investigation revealed that xxxxxx batch were checked for thickness and were within specification. As per the batch record, the operator also checks the xxx for hardness and xxx aggregate weight and appearance. (Exh. 2a2 p.25) No deviations were noted. The batch record contains notes of the stop and restart on 11/19/07; however, it seems that the equipment is stopped at xxx, restarted at xxx, and then there are additional notations that the machine was stopped and started for QA approval at xxx. The only QA approval for start up on xxx (Exh. 2a2 p. 28, 37-38) (Ref 14 p. 23)

"As per the batch record, Quality Assurance takes xxxx from each exit chute xxxx station of the press), "at start-up and periodically test samples while in process to verify weight, thickness, and hardness of each sample." Review of the executed batch record revealed that the start-ups, thickness, hardness and weight checks by QA are documented as (Exh. 2a3 pp.35-58). (Ref 14 p. 23)

"The investigation did not evaluate the possibility of sticking problems, formulation problems, equipment/ tooling problems, operator error, metal detector or deduster problems or other potential sources of "double thick" tablets. No explanation was provided for the failure to chemically analyze the tablets or to evaluate the thickness or weight of all tablets to determine a root cause. I asked Ms. Lambridis and Mr. Talbot how they could assure that other tablets within the batch were not out of specification when the routine checks by the operator and Quality Assurance did not identify the defect, as evidenced by the double thick tablets being found during packaging. Ms. Lambridis and Mr. Talbot could not provide any evidence to assure that additional out of specification tablets would not be identified if inspection by

thickness, weight, or chemical analysis was conducted. We also discussed the failure to evaluate other lots and strengths due to the lack of root cause for the defect. (Ref 14 p. 23)

"We noted during a review of the record packaging of the product that the initial lot xxxx resulted in xxxxx (Exh. 2a2 p. 136). Following the inspection process, the product was repackaged as and resulted in xxxx (Exh. 2a2 p. 138). We noted the discrepancy and stated.th5lt despite the removal of the xxx "double thick" tablets found and the AQL sampling, there was an additional bott1e of 1000.tablets that resulted. We discussed the finding with Scott Talbot and asked if the discrepancy was investigated. He stated that it was not. He noted that perhaps the counts were within tolerance but slightly different than the first packaging run for the product. No further explanation was provided. (Ref 14 p. 24)

"The visually inspected repackaged product was released by the Quality Unit on 1/28/08 xxxxx (Exh. 2a3 p. 6). A documentary sample, DOC 419935 was collected to document the cGMP deficiencies observed for the product. (Ref 14 p. 24)

"Tablets are indicated for use as å "cardiac ionotropic and anti-arrhythmic agent indicated for the treatment of mild to moderate heart failure" (Exh. 2 a4 p. 1).They are taken daily and are considered a low dose with a narrow therapeutic index. The product is contract manufactured for xxxxxx. A health hazard evaluation was not conducted at the time of inspection, but was generate on 4/18/08 by a contractor xxxx hired by Actavis Medical Affairs to "evaluate the impact of Digoxin Tabs 0.125mg at were had a thickness approximately double to that required." (Exh. 2a4 p. 1). The conclusion by xxxx the health hazard assessment is as follows: (Ref 14 p. 24)

"Potential risks to the patient depend on the constituency of the tablets. If the tablets contain double the dose (0.250 mg), then it can be expected that digitalis toxicity can occur in individuals taking daily doses or in patients with renal insufficiency. Toxicity can include nausea, vomiting, dizziness, low blood pressure, cardiac instability and bradycardia. Death can result from excessive digitalis intake. If increased thickness is due to clinically inert substances, then a disease (congestive heart failure and arrhythmia) due to lack of therapeutic efficacy." (Exh. 2a4) (Ref 14 p. 24)

"Investigator Zielny and I, Investigator McCaffery, notified New Jersey District Management of the findings during the inspection due to the potential health hazard associated with patients receiving Digoxin Tablets with double the thickness. We also notified the firm's upper management in a meeting on 4123/08 regarding the firm's plans for organizational changes and corrective actions. Following the meeting, the documentation of the commitments was provided (Exh. 14). Following discussions with CDER's Office or Compliance, District Management contacted Robert Wessman., CEO Actavis Group on 4/24/08 to discuss the impact on other lots of Digoxin Tablets on the market Mr. Wessman provided a verbal commitment to recall all lots of Digoxin 0.125mg and 0.250mg Tablets 0'0 4/24/08. There were xxx Digoxin 0.250mg Tablets on the market at the time of the recall. (Ref 14 p. 24)

SECTION DELETED

"OSBSERVATION 3 (Ref 14 p. 27)

"The numerous stability out of specification results were discussed throughout the inspection with Ms. Lambridis and in meetings with the firm's upper management. We stated that the response to the results was reactive based on our inspectional findings. It did not assure us that the Quality Unit and Quality System could identify and address product quality issues in a timely manner. We acknowledged the improvements in the laboratory such as the use of audit trails, independent data reviews, and notification to the Quality Unit of the out of specification results. We stated that the manufacturing and Quality Assurance investigations were not timely or were not conducted. We also acknowledged the firm's explanation that many products were

placed in ICH stability conditions for the first time in 2005 which may have contributed to the numerous out of specification results. There is no assurance that other products which were not reviewed during our inspection will not have similar issues. Risk assessments were not conducted the products which remain on the market or the products which are retained in the distribution centers that were made with the oversight of the same Quality Unit. At the exit meeting, I, Investigator McCaffery, and Supervisory Investigator Harlan reiterated our concern for other products which were not evaluated as part of our inspection. During the exit meeting discussions, Mr. Wessman acknowledged the need for immediate and timely corrective action. He provided verbal and written commitments as "documented. in "ADMINISTRATIVE DATA", "GENERAL DISCUSSIONS WITH MANAGEMENT" and "VOLUINT.ARY CORRECTIONS" sections of this report. Reference: 21 CFR 211.192 (Ref 14 p. 27)

"OBSERVATION 4 (Ref 14 p. 43)

"Determinations of conformance to appropriate written specifications for in-process materials are deficient for in-process materials. (Ref 14 p. 43)

"Specifically,

"Although three out of specification results were obtained for blend uniformity at the "Right-Top" sample location for Digoxin Tablets 0.125 mg, lots# 70148A (OOSN07-016), 70207A, (OOSN07-022) and 70770A (OOSN07-116) on 2/2/07, 3/14/07 and 9/29/07; no manufacturing investigations were conducted. Additional samples were used to retest the blend and were reported. Lot# 70207Al was released on 6/7/07 and lot# 70770Al was released on 11/30/07 by the Quality Unit. Lot# 70148A was not released due to atypical content uniformity results. (Ref 14 p. 43)

"In reviewing the 2007 Annual Product Review for Digoxin Tablets 0.125 mg, I, Investigator Zielny, noted that three of the five OOS Investigations were initiated due to out of specification results in blend uniformity upon reviewing the three OOS namely (Exh. 4a2) for batch # 70148A (Exh. 4a3) for batch #70207A, and xxx for batch # 70770A 9Exh 4a4), I noted that all three batches failed to meet blend uniformity specifications due to a low result at the same sample point. Specifically, out of specification results for blend uniformity were obtained due to low results received at the "Right-Top" sample location in the blend uniformity testing of Digoxin Tablets 0.125 mg lot 3s 70148A on 2/20/07, 70207A on 3/14/07 and 70770A on 9/29/07. The blend uniformity test specifications for batch #s 70148A and 70207a were Individual xxx. RSD: NMT xxxx and the specifications for batch #70770A were Average xxx RSD: NMT xxx (See FDA-483 observation 4C for further information regarding changes in blend uniformity testing specification.) The results for the "Right-Top" sample for the above mentioned batches are as follows: (Batch xxx Exh. 4a5, 4a6, 4a7) (Ref 14 p. 43-44)

"When samples were pulled for blend uniformity testing, duplicate samples were taken from the same sample locations. The testing of the duplicate les of xxxxx and xxxxx was performed and the results were reported. For xxx triplicate samples had been taken from the same locations for blend uniformity testing. Sample set-2 and set-3 were tested and were within specification. The results from all three sets were reported for batch # 70770A. No manufacturing investigations were conducted into the original failing results any of the three batches. (Ref 14 p. 44)

"The OOS Investigation regarding xxxx indicated that "the blend is considered acceptable for however as an additional measure xx additional samples be taken to uniformity and acceptability prior to release to the market." A planned deviation, xxx (Exh. 4a8) was initiated in order to request an additional xxx throughout compression of the batch for content uniformity testing. Although the additional content uniformity testing met specification, a final decision to reject batch # 70148A was made because "no root cause was identified and the content uniformity results were not conclusive. This decision to reject the batch can be seen on page 2

of Exh. 4a8. Xxxx. Finished Product and Stability Testing explained that the inconclusive content uniformity results were referencing the fact that the original content uniformity testing went to the L-2 testing because the content uniformity testing of the first ten tablets resulted in an acceptance value of xxx whereas specification is xxx (Exh. 4a9, p. 4). Exhibit 4a9 shows the original content uniformity testing, the L-2 testing and the testing of the additional xxx as required by xxx. The L-2 testing passed specification of acceptance value. Xxx stated that the rejection of the batch was die to 1) the fact that original content uniformity testing went to stage-2 (L-2) and 2) a difference was observed between the results received during the original content uniformity testing and the results received for content uniformity testing of the additional xxx Lot # 70148A1 was rejected on 7/23/07 (Exh. 4a10), four months after the initiation of the planned deviation to perform additional content uniformity testing. (Ref 14 p. 44)

"Batch # 70207 A also had a planned deviation associated with the batch in order to perform content uniformity testing on an additional taken throughout compression. The additional samples met specifications and lot # 70207Al was released for shipment on 6/7/07. Copies of the compression release, bulk product disposition form, batch record review and finished product release form are attached as Exh. 4a11. (Ref 14 p. 45)

"Batch # 70770A did not have a planned deviation associated with the batch. No answer could be provided as to why the first two OOS blend uniformity investigations included provisions for additional content uniformity testing and this investigation failed to initiate a similar planned deviation. Lot # 70770Al was released for shipment on 11/30/07 without additional content uniformity testing. Copies of the compression release, bulk product disposition form, batch record review and finished product release form are attached as Exh. 4a12. (Ref 14 p. 45)

SECTION DELETED

"Although approximately xx products were "temporarily discontinued" due to blend and/or content uniformity issues, there was no rationale provided for the blend uniformity specifications from xxxxxxxxxxxxxxx. (Ref 14 p. 45)

"During the inspection, we were provided a list of products that have been temporarily discontinued (Exh. 4c.1). The list includes "blend issues" as the reason for the temporary discontinuation in the production 'of Betaxolol Tablets, USP 10 mg, Carisoprodol, Aspirin and Codeine Phosphate Tablets, USP 200mg/325mg/l6mg, Ch1or-timetron, Drixoral Cold & Allergy Extended Release Tablets and Hydrocodone Bitartrate and Homatropine Methylbromide Tablets 5mg/l.5mg. Despite noted "blend uniformity issues", in-process blend uniformity calculations for many products were changed for xxxx (individual) RSD NM : xxxx (average) xxxxxx Current in-process uniformity specifications for this following products are listed xxxxx (Average) (Exh. 4c2): SECTION DELETED Digoxin Tablets, USP 0.125 mg and 0.25 mg SECTION DELETED (Ref 14 p. 46)

"The list of "temporarily discontinued products" also indicates that three of five products with blend issues also had content uniformity issues. The products included: Betaxolol Tablets, USP, 10 mg, Chlor-Trimeton Tablets, and Drixoral Cold & Allergy Extended-Release Tablets (Exh. 4c1). However an "interim report for xxxxx discusses blend uniformity issues with 17 batches and concludes that the "the recent trend or product blend in 2007 was to the sample handling of the slugging the blend samples' and the testing of blends and was not due to a shift in manufacturing practices" (Exh. 4c3). No scientific rationale could be provided for changing in-process blend specifications form xxxx. SECTION DELETED (Ref 14 p. 46-47)

"OBSERVATION 6 (Ref 14 p. 54)